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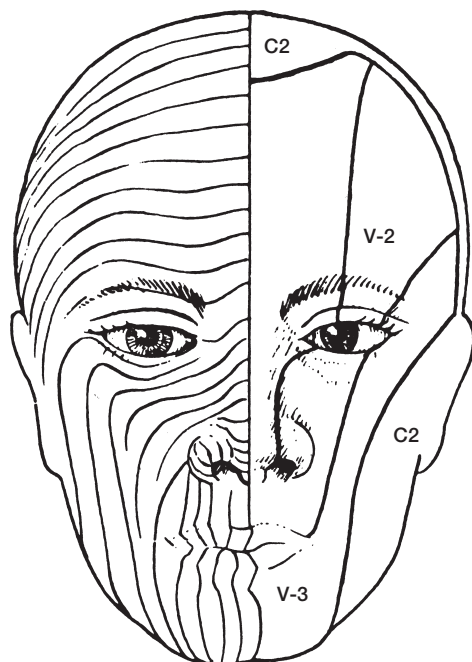
Manual of Dermatologic Therapeutics

8TH EDITION

Kenneth A. Arndt,
Jeffrey T.S. Hsu, Murad Alam,
Ashish Bhatia, Suneel Chilukuri



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Left side: Relaxed skin tension lines. *Right side:* Dermatome chart—sensory root fields.

Note: The illustrations on the inside covers and facing front cover, dermatome charts and relaxed skin tension lines (RSTLs), represent approximations, since there is much overlap and individual variation. Denervation of one posterior root will not produce complete anesthesia within the corresponding dermatome. The direction of the RSTLs should always be assessed before making an ellipsoidal incision parallel to, or a punch biopsy with skin stretched perpendicular to, these lines (see Fig. 48-1, p. 370). In areas of flexion creases, flex and note the direction of the majority of “wrinkle” lines, that is, the direction of the RSTL. In nonflexion areas, the RSTL is determined by picking up skin folds between the thumb and index finger and pinching, proceeding in a clockwise direction, until it is clear in which direction wrinkle lines are most numerous, straight, and parallel to one another. In certain areas it is difficult or impossible to find the RSTL. In that situation, make a small circular incision or “punch” to see in which direction the ellipse forms.

MANUAL OF DERMATOLOGIC THERAPEUTICS

Eighth Edition

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To my family, with love.

Kenneth A. Arndt

To Mom, who teaches me to always do good. To Anita, who challenges me to always do better.

Jeffrey Hsu

Many thanks to all those that inspire and support me: my Mom & Dad, teachers, my loving family, my dear friends, my entire team at the office, my brilliant partners in practice—Jeff & Kelly, and my ever patient wife Tania.

Ashish C. Bhatia

To my parents, Rahat and Rehana; my sister, Nigar; my nephew, Ali; my niece, Noor; MP and BT, and Dr. Arndt, who always made us feel worthy and inspired us to be better.

Murad Alam

Thank you, Mom & Dad, for giving me the tools to succeed. Thank you Susan, Sonia, and Sage for your patience and allowing me to use these tools. With love.

Suneel Chilukuri

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Preface

When the first edition of the Manual was published in 1974, I could not have imagined how this set of guidelines to the treatment of common skin disorders would evolve into its current form. With the 2014 edition, the Manual is reframed and it is now a bigger, enhanced, and more colorful print and electronic publication. My original goal in creating the Manual was to present rational and practical therapeutic guidelines that would be useful for physicians and other health-care personnel. The original publication and the subsequent editions were greeted with enthusiasm and they became widely used in the United States and throughout the world through Spanish, Portuguese, Italian, Indonesian, French, and Chinese versions.

The understanding of the causes, course, and therapy of cutaneous disorders has changed dramatically over the past four decades, as has the whole field of dermatology and the biology of skin disease. The procedural aspects of the specialty have broadened enormously as has the expertise and interest in dermatologic surgery. As knowledge about the pathophysiology of the skin and the basis of cutaneous disorders has become better understood, sophisticated and highly effective therapies for many disorders have become available, such as the biologic agents in the treatment of psoriasis. The specialty has become bigger, broader, and better, and so has this Manual.

The structure and style of this edition were conceptualized together with my colleagues and coeditors Murad Alam, Ashish Bhatia, Suneel Chilikuri, and Jeffrey T.S. Hsu. Jeff Hsu assumed the yeoman task of pulling this all together and has been the driving force behind the successful completion of this edition. The book has been enlarged and enhanced with discussion of all common and many less common disorders affecting the skin. Each chapter has been edited, rewritten, or newly written by authors from around the country, particularly from the Departments of Dermatology at the University of Chicago, Northwestern, Baylor, and Yale Universities, and was then reviewed by several of the coeditors, Dr. Hsu and myself. For each entity, the Background is first discussed, followed by sections on the Clinical Presentation, Workup, Treatment, References, and Suggested Readings. Included are tables listing treatment choices and differential diagnosis and numerous color illustrations. As in previous editions, there are sections on Operative Procedures, Diagnostic and Therapeutic Techniques, and Treatment Principles.

We hope that the eighth edition of the Manual is as helpful and educational a guide to rational therapeutics and disease management as the previous seven editions have been.

Kenneth A. Arndt

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I. BACKGROUND Acne vulgaris is a common, chronic disorder, involving inflammation of the pilosebaceous units that can be varied in presentation and difficult to treat. Acne pathogenesis derives from four main factors: sebaceous gland hyperplasia, abnormal follicular desquamation, *Propionibacterium acnes*, and inflammation. The primary lesion is the microcomedo, which may evolve into a noninflammatory comedo (open or closed) or become inflamed and form a papule, pustule, or nodule (Figs. 1-1 and 1-2).

Most adolescents (80%) experience some acne; however, it may linger into adulthood. Lesions may begin as early as ages 8 to 10 years at adrenarche, when androgens of adrenal origin begin to stimulate pilosebaceous units. Severe disease affects boys 10 times more frequently than girls, and patients often have a family history of severe cystic acne (Fig. 1-3).

Neonatal acne or cephalic pustulosis is self-limited with an onset around 2 to 3 weeks of age. Nearly one in five newborns is affected by at least mild neonatal acne characterized by erythematous nonscarring papules on the face and neck, most commonly on the cheeks and nasal bridge. This disorder spontaneously resolves within 1 to 3 months. *Malassezia* spp. have been implicated in the pathogenesis of neonatal acne. Topical 2% ketoconazole cream as well as benzoyl peroxide (BPO) has been shown to be effective treatments, although parental reassurance alone is often sufficient, given the transient and benign nature of the eruption.

Infantile acne usually presents at 3 to 6 months of age and includes persistent comedones and inflammatory lesions with an increased risk of scarring. Immature infantile adrenal glands lead to elevated dehydroepiandrosterone (DHEAS) levels until the age of 12 months. Boys are more often affected than girls because of additional high testosterone levels between the ages of 6 and 12 months. Infantile acne usually resolves within 1 to 2 years; however, individuals with infantile acne may have an increased risk of severe acne as teenager's acne. Acne in mid-childhood is relatively uncommon and may be a marker for adrenal or gonadal tumors. Further workup of these patients is advised.

Early-onset acne may be the first sign of an underlying hormonal abnormality, especially if there is an associated advanced bone age and early pubic hair development. At puberty, hormonal stimuli lead to increased growth and development of sebaceous follicles. Female patients with severe acne or evidence of virilization often have abnormally high levels of circulating androgens. Several studies have demonstrated that many female patients with milder forms of acne and no evidence of virilization may still have ovarian and/or adrenal overproduction of androgens. In those patients with normal circulating levels of androgens, there is some evidence that suggests a heightened end-organ responsiveness of the sebaceous glands to androgenic stimulation. This heightened end-organ response may result in increased conversion of testosterone to



Figure 1-1. Noninflammatory lesions. The combination of open (blackheads) and closed (whiteheads) in a young patient. (With permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 1-2. Inflammatory acne lesions. Papules, pustules, and closed comedones are all present on this patient. (With permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

dihydrotestosterone and other 5- α -reduced metabolites or suppressed follicular testosterone metabolism. Male acne patients tend to have higher levels of androstenedione, testosterone, free androgen index, and 11-deoxycortisol.¹

As many as one-third of adult women are affected by a low-grade acneiform eruption that may start *de novo* or merge imperceptibly with preexisting adolescent acne. The eruption may be induced by chronic exposure to

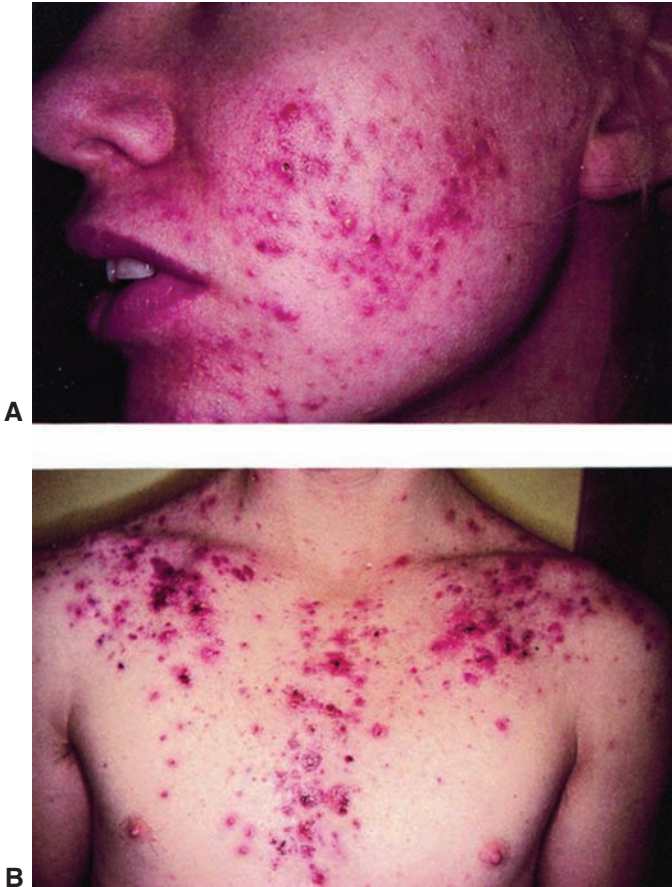


Figure 1-3. Severe nodulocystic acne with scars on (A) face and (B) chest. (With permission from Hall JC. *Sauer's Manual of Skin Diseases*. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999: 118 p.)

comedogenic substances such as isopropyl myristate, cocoa butter, and fatty acids present in some creams and moisturizers, by androgenic stimuli from progestins present in some oral contraceptives, by recent cessation of oral contraceptives, or by unknown causes.

Inflammatory acne may yield both scarring and pigmentary changes. Early treatment is essential to prevent and minimize the cosmetic disfigurement associated with acne scarring. Adequate therapy will, in all cases, decrease its severity and may entirely suppress this disease.

II. CLINICAL PRESENTATION Acne has a significant impact on the patient's self-image and quality of life, and the psychological toll of acne may be comparable to that of asthma or epilepsy. Even clinically mild acne may

cause considerable social embarrassment to the patient. As with all medical and psychological conditions, the patient's perception of the severity of the problem is an important factor in choosing treatment.

- A. Noninflammatory Lesions.** The initial lesion is the closed comedo; visible as a 1- to 2-mm white bump (whitehead) most easily seen when the skin is stretched. If follicle contents extrude, a 2- to 5-mm, dark-topped, open comedo (blackhead) results. Patients should be advised that this black material is simply oxidized keratin, not dirt.
- B. Inflammatory Lesions.** Erythematous papules, pustules, cysts, and abscesses may be seen. Patients with cystic acne also tend to show polyporous comedones, which result from prior inflammation during which epithelial scarring caused fistulous links between neighboring sebaceous units. Acne lesions are seen primarily on the face, but the neck, chest, shoulders, and back may be involved. One or more anatomic areas may be involved in any given patient, and the pattern of involvement, once present, tends to remain constant.

III. WORKUP Several points regarding etiology or therapy should be considered with each patient:

- A. Endocrine Factors.** Sudden onset of acne, treatment-resistant acne, and acne associated with signs of androgynism should lead one to suspect an endocrine abnormality.

1. Acne Accompanied by Irregular Menstrual Periods or Concomitant

Hirsutism. Men and women with mild-to-severe cystic acne, especially those who do not respond to conventional therapy, may have elevated plasma-free testosterone and/or DHEAS levels. Hyperandrogenism is associated with acne, hirsutism, alopecia, and menstrual irregularities; other possible findings include infertility, deepening of the voice, increased libido, acanthosis nigricans, insulin resistance, type 2 diabetes mellitus, and dyslipidemia. DHEAS elevations above 8,000 ng/mL suggest the presence of an adrenal tumor; a range of 4,000 to 8,000 ng/mL is indicative of congenital adrenal hyperplasia. Testosterone elevations point to an ovarian dysfunction, with levels of 150 to 200 ng/dL suggesting an ovarian tumor. Oral contraceptives can mask an underlying endocrine disorder, so testing should be done 1 month after the discontinuation of exogenous hormones. Women may have high normal levels of DHEAS and testosterone and may benefit from hormonal therapy. Postmenopausal acne occurs in some women with previously oily skin, with the development of small closed comedones at the periphery of the face; unopposed adrenal androgens are the presumed cause. See Table 1-1.

2. Premenstrual Flare-Up. Premenstrual flares of acne are associated with a narrowing of the sebaceous duct orifice between days 15 and 20 of the menstrual cycle. This can lead to duct obstruction and resistance to the flow of sebum. Many women tend to do well on anovulatory drugs.

3. Acne Associated with Oral Contraceptives. Acne may be associated with oral contraceptive pills if recently started or discontinued and if composed of an androgenic progesterone. During the first two or three cycles

TABLE 1-1

Endocrinopathies to Consider in Patient with Acne

- Stein-Leventhal syndrome
- Cushing syndrome
- 21-Hydroxylase deficiency
- Polycystic ovarian syndrome (Fig. 1-4): defined by menstrual irregularities, acne, pelvic ultrasound imaging of subcapsular ovarian cysts, and an elevated luteinizing hormone to follicle-stimulating hormone ratio (a level greater than two to three is suggestive). The testosterone elevations are modest in the range of 80–150 ng/dL



Figure 1-4. Hirsutism related to polycystic ovary syndrome. This is the most common cause of androgen excess and hirsutism. Note the lesions of acne. (With permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

on oral contraceptives, acne may worsen. Post-pill acne may continue for as long as a year after birth control pills are stopped. Although anovulatory drugs may provide excellent therapy for acne, the various pills differ enormously in their effect on the sebaceous gland. Oral contraceptives that contain the androgenic and antiestrogenic progestogens norgestrel and norethindrone acetate may actually provoke an acneiform eruption.

B. Acne due to Occupational or Chemical Exposure. Exposure to heavy oils, greases, polyvinyl chloride, chlorinated aromatic hydrocarbons, and tars can cause acne. These occlusive comedogenic agents will initiate lesions, as can some greasy substances used for hair care (pomade acne). Certain oily or greasy cosmetics and creams can also exacerbate acne.

C. Acne due to Occlusive Clothing or Habits. Mechanical trauma (pressure, friction, rubbing, and squeezing) from clothing or athletic wear or from behavioral habits will also cause lesions. For example, football players may develop acne lesions in the distribution of their helmet and chin strap.

D. Medications-Induced Acne. Drug-induced acne often presents as an abrupt, monomorphic eruption of inflammatory papules. The most prominent among these are corticosteroids, adrenocorticotrophic hormone, phenytoin, androgens, anabolic steroids (danazol and testosterone), epidermal growth factor receptor inhibitors, and melanoma chemotherapy agents such as Vemurafenib. Other known stimuli include trimethadione, isoniazid, lithium, iodides, bromides, halothane, vitamin B₁₂, cobalt irradiation, and hyperalimentation therapy.

E. Rapid-Onset Acne Associated with Fever and Leukocytosis. Acne fulminans is a destructive arthropathy, resembling rheumatoid arthritis. SAPHO syndrome consists of synovitis, acne, pustulosis (palmar–plantar pustular psoriasis), hyperostoses, and osteitis; this is considered one of the spondyloarthropathies and has been reported with inflammatory bowel disease (IBD) and pyoderma gangrenosum. The PAPA syndrome, an autosomal dominant disorder, consists of pyogenic sterile arthritis, pyoderma gangrenosum, and acne.

F. Antibiotic-Resistant Acne. There is an increased incidence of bacterial resistance of both *P. acnes* and coagulase-negative *Staphylococcus aureus* noted after long-term antibiotic use. These resistant bacteria are found in both the patients and their close contacts. *Propionibacterium acnes* resistance to antibiotics should be considered in treatment failures. This is seen particularly with erythromycin; but cross-resistance can occur with clindamycin. Multiple antibiotics should not be used at the same time and BPOs should be added as a second agent to help minimize this possibility. The highest possible dose of an oral antibiotic should be started for as short a course as possible. Oral minocycline has the lowest risk of bacterial resistance over time. Oral isotretinoin reduces the total number of resistant *P. acnes*.

An unusual complication of chronic broad-spectrum antibiotic therapy is the development of a gram-negative folliculitis. Such patients will notice a sudden change in their acne, with the appearance of pustules or large inflammatory cysts that, on culture, usually grow *Proteus*, *Pseudomonas*, or *Klebsiella* species. Because acne cysts are sterile on routine bacteriologic culture, a sudden change in morphology warrants Gram stain and culture of cyst/abscess contents. This condition is treated with isotretinoin or the appropriate antibiotic determined from culture and sensitivity testing.

IV. TREATMENT Acne therapy must take into consideration a multitude of factors. Often multiple therapeutic agents are used simultaneously or on a rotation schedule depending on patient response and side effects. The treatment of acne is a dynamic process and must always include the patient's subjective evaluation of his or her appearance and symptoms.

A. Topical Retinoids are the first-line treatment for acne and represent one of the most effective groups of drugs. A small percentage of patients may experience a pustular flare of their acne in the first few weeks of topical retinoid therapy, a transient effect that is indicative of the effectiveness of therapy. Tazarotene is labeled as category X, on the basis of its indication for psoriasis when larger areas with an altered skin barrier are treated. Tretinoin and adapalene are category C. Minimizing exposure to sunlight and sunlamps is advised with the use of all retinoids because of an increased susceptibility to burning, likely secondary to the thinning of the stratum

corneum. Patients should be given specific instructions on applying retinoids (Table 1-2).

1. **Tretinoin** (*trans*-retinoic acid; vitamin A acid) first became available 25 years ago. The irritant effects of tretinoin sometimes limit its usefulness, but these can be minimized by the correct method of application. Tretinoin increases epidermal cell turnover and decreases the cohesiveness of cells, thereby inhibiting the formation of comedones while helping existing comedones to loosen and be expelled. Tretinoin also decreases the number of normal cell layers of the stratum corneum from 14 to 5. This decrease in the thickness of the barrier layer may potentiate the penetration of other topical agents.
2. **Adapalene** is a derivative of naphthoic acid and a selective retinoic acid analog. This product is not degraded by sunlight, is not phototoxic, and is compatible with BPO application at the same time. When compared with topical tretinoin 0.025% gel, there is a lower incidence of cutaneous irritation and it compares favorably in the reduction of both inflammatory and noninflammatory lesions. This effect may be secondary to its more selective binding, increased lipophilic properties, and follicular penetration. This is a good first-line therapy in colder climates or in patients with sensitive skin.
3. **Tazarotene** is a potent selective retinoid that binds to the retinoic acid receptors, RAR- β and RAR- γ . This drug is converted in the epidermis to its active metabolite tazarotenic acid and was originally developed

TABLE 1-2 **Instructions for Retinoid Use**

The cream base is preferred for dry skin and the gels are preferred for oily skin. The strength of the product may be gradually increased once the patient has become tolerant of the weaker formulation.

- a. Apply sparingly every other night to the entire face except around the eyes, lips, and neck. After 2–3 wk, if no excess irritation, erythema, dryness, or scaling is noted, increase to every night. Tazarotene is best applied over or several minutes after the application of a moisturizer at bedtime.
- b. Use mild, gentle soaps not more than twice daily.
- c. Avoid excessive exposure to sun. Use sunscreens.
- d. Use water-based cosmetics if necessary.
- e. Expect mild redness and peeling within a week, lasting 3–4 wk, and a flare-up in the acne during the first 2–4 wk. This is explained to the patient as the surfacing of lesions onto the skin.
- f. Clearing requires approximately 3 mo. Inflammatory lesions improve more rapidly, but comedones take longer. Effectiveness cannot be judged before 8 wk and is best assessed at 12 wk.
- g. Continue retinoid application after the lesions clear.
- h. Apply less frequently if the daily use of the retinoid cannot be tolerated—for example, every other night or skipping every third night.
- i. Although there is negligible systemic absorption of topical retinoids, this agent should be discontinued if pregnancy is suspected. Cases of neurologic toxicity and ear malformation have been reported.

for the treatment of psoriasis. Tazorac is a category X drug and must be avoided in pregnancy. This drug can be irritating and should be avoided in patients with sensitive skin or seborrheic dermatitis. The 0.1% gel is more effective than the 0.05% concentration; however, starting with the 0.05% concentration may decrease the irritation. Some investigators advocate short-contact therapy, such as 1- to 5-minute exposures every other night, especially for patients with resistant comedones. Treatment time can be gradually increased to overnight. Twice-daily short-contact therapy can be tolerated in the individual with an oilier complexion. This product is not degraded by sunlight.

B. Topical Antimicrobials. Bacteriostatics can be applied twice daily to the point of mild dryness and erythema, but not discomfort.

1. **BPO** has a potent bacteriostatic effect with a reduction of *P. acnes* within 2 days and a reduction in lesion count after 4 days of application. BPO decreases the likelihood of bacterial resistance and should be a mainstay of every acne program, if tolerated. It is hypothesized that this agent is decomposed by the cysteine present in skin, after which free-radical oxygen is capable of oxidizing proteins in its vicinity. These proteins include the bacterial proteins of the sebaceous follicles, thereby decreasing the number of *P. acnes*. Contact sensitivity is observed in 1% to 3% of patients. BPO can bleach the color out of clothing. BPO products are now largely over the counter, with numerous brands available, varying in strength from 2.5% to 10%.
2. **Topical Antibiotics** may affect acne lesions by their bacteriostatic action or because of suppressive effects on the inflammatory response. Papular and pustular lesions respond best; the activity of comedonal or cystic acne may not be altered. Resistant organisms may emerge after continued therapy; combination therapy with BPO minimizes this risk. All topical antibiotics are applied twice daily.
 - a. **Clindamycin Phosphate** is available in 1% concentration in a hydroalcoholic vehicle (30 or 60 mL) as a gel or lotion. There have been two reports of pseudomembranous colitis after topical use of clindamycin hydrochloride. Patients with IBD should avoid topical clindamycin use, and all patients should be warned to discontinue therapy if intestinal symptoms occur. Products that combine clindamycin with BPO include BenzaClin and Duac.
 - b. **Erythromycin Base** applied topically has been a mainstay in treatment of acne. However, widespread resistance has now limited its use as a monotherapy. Its primary advantage lies in its safety in pregnant patients.
3. **Salicylic Acid** is a β -hydroxy acid that penetrates into the sebaceous gland and has comedolytic and anti-inflammatory properties. It can be used as an adjunctive therapy and is found in cleansers, toners, masks, and peels. Its side effects include erythema and scaling.
4. **Azelaic Acid** is a dicarboxylic acid that has antimicrobial, anti-inflammatory, and comedolytic activity, and it is relatively nonirritating. It is available as a cream (Azelex) or gel (Finacea) formulation. Azelaic acid may help lighten postinflammatory hyperpigmentation and is a good choice for ethnic or pigmented skin. It is not a photosensitizer and so far shows minimal tendency for bacterial resistance. This drug works best

when combined with other topical preparations, for example, BPOs and retinoids.

5. **Topical Dapsone** is useful in reducing inflammatory acne, although the exact mechanism is unknown. It should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency. Topical dapsone is pregnancy category C.

C. Combination Therapy. In combination therapy, the retinoid prevents or removes comedones, whereas BPO or topical antibiotic eradicates *P. acnes*. The retinoid also enhances absorption of the other product. Irritation reactions may limit the use of this combination therapy in some patients. Combinations may be composed of two or more separate single agents, or a branded combination product (Table 1-3).

D. Systemic Antibiotics. The beneficial effects of antibiotics are multifold. Not only are the number of bacteria and free fatty acid (FFA) levels decreased, but antibiotics useful in acne therapy also directly interfere with local chemical and cellular inflammatory mechanisms. Tetracycline, erythromycin, and clindamycin have been shown to inhibit leukocyte chemotaxis and other neutrophil inflammatory functions and may also directly inhibit extracellular lipases responsible for the generation of inflammatory compounds. Antibiotic therapy cannot be truly evaluated until 6 to 8 weeks after starting. Antibiotic levels in sebum are not detectable until approximately 7 days after treatment has started, and lipid formed in basal cells of sebaceous follicles may require 1 month to reach the skin surface. Although sebum composition changes, the rate of secretion remains constant; therefore, skin may remain oily. Therapy may need to be continued for several months. It is controversial whether to taper the oral antibiotics or to stop with no taper. Tapering may allow resistant organisms to grow more readily, while a sudden stop may lead to acne flare. Long-term use of antibiotics likely contributes to the pool of resistant organisms.

1. Tetracycline Derivatives

a. Minocycline is overall the most effective antibiotic available to treat acne, but it can have serious side effects. This antibiotic is very lipid soluble and penetrates the sebaceous follicle more effectively; it is well absorbed, even with meals. Owing to its highly lipophilic nature, it crosses the blood–brain barrier and can precipitate pseudotumor cerebri syndrome. The duration of therapy can be a week to a year, with the most common presenting symptoms being headache, visual disturbances, diplopia, pulsatile tinnitus, nausea, and vomiting.

Because minimal amounts of minocycline remain in the gut, the frequency of *Candida* vaginitis is less than in those taking tetracycline.

TABLE 1-3 **Examples of Branded Combination Topical Treatments**

1. BPO and retinoid: Epiduo
2. Retinoid and antibiotic: Veltin, Ziana
3. BPO and antibiotic: Acanya, BenzaClin, Benzamycin, Duac

BPO, benzoyl peroxide.

Most tetracycline-resistant bacteria are sensitive to minocycline at a dose of 100 mg b.i.d. Dizziness, nausea, and vomiting may be a problem if full doses are administered initially. Start at 50 mg/day and slowly increase to as much as 100 mg b.i.d. Some patients may eventually achieve complete control on 50 mg/day.

Minocycline may cause a blue discoloration of acne cysts or sites of trauma; this discoloration usually does not appear until 8 months of therapy with a total cumulative dose of 70 g and is usually reversible after discontinuation of the drug, though resolution is exceedingly slow. Once a cumulative dose of 100 g is reached, alternative therapies should be considered. Cases of autoimmune hepatitis, serum sickness-like reactions, pulmonary infiltrates with eosinophilia, and a syndrome similar to drug-induced lupus have been reported secondary to minocycline. All symptoms resolve with discontinuation of the drug. The estimated risk is an 8.5-fold increase from controls, an absolute risk of 52.8 cases/100,000 prescriptions.² If long-term minocycline is taken (i.e., >2 years), periodic liver function tests (LFTs) and antinuclear antibody levels may be warranted. A personal or family history of systemic lupus erythematosus or underlying liver and/or kidney disease may be relative contraindications to the use of this drug.

- b. Doxycycline** has similar absorption and duration-of-activity characteristics as minocycline. Its effectiveness in acne approaches that of minocycline, when used in the same manner with similar dosages. Early data suggest that subantimicrobial doses of doxycycline, 20 mg (Periostat), may play a therapeutic role in acne by reducing inflammation through anticollagenolytic, antimatrix-degrading metalloproteinase, and cytokine downregulating properties. Patients taking doxycycline must be warned to avoid excessive exposure to sunlight because of the photosensitivity that accompanies the use of this drug. Patients should be advised to take pills with food and a full glass of water, to avoid erosive esophagitis. The evening dose should be taken at least 30 minutes prior to lying down for bed. Patients who are unable to sit for at least 30 minutes are poor candidates for this medication. A history of gastric ulcers is also a relative contraindication.
- 2. Erythromycin**, 1 g/day, is also effective in the treatment of acne. The same dose and time responses noted for tetracycline also apply for this drug. However, given up to 40% of *P. acnes* organisms are now resistant to erythromycin, combination with topical BPO may help decrease bacterial resistance. Elevated LFTs and reversible hepatotoxicity have infrequently been reported.
- 3. Clindamycin**, 300 to 450 mg/day, is an effective agent for acne. However, the risk of pseudomembranous colitis limits its systemic use to only very severe cases that are unresponsive to all other modes of therapy.
- 4. Trimethoprim-Sulfamethoxazole** has also been shown to decrease FFA levels and inhibit inflammatory acne. Trimethoprim is very lipophilic, which enhances follicle penetration. Start with one double-strength tablet at bedtime; up to two tablets per day may be used. A high rate of allergic reactions limits its use. Neutropenia may occur on long-term

therapy, and a baseline complete blood count with intermittent monitoring is recommended. Toxic epidermal necrolysis is unlikely to occur after the first month of therapy. Cases of hepatic necrosis and aplastic anemia have also been associated with this drug.

5. **Ampicillin** may also be helpful in certain patients. In resistant acne patients, culture may reveal gram-negative bacteria responsive to ampicillin.
6. **Azithromycin** in a 500-mg dose three times a week has been shown to yield a 60% reduction in inflammatory papules in 83% of patients enrolled in a 12-week study.³

E. Sebaceous Gland Suppression

1. **Oral Contraceptives** (estrogen given as an anovulatory agent) may be of use in unresponsive cases in young women after more conventional regimens have failed. If a patient with acne is already taking anovulatory agents for contraception, an effort should be made to use a formulation known to alleviate, rather than exacerbate, acne. Most or all the estrogen effect is the result of adrenal and androgen inhibition rather than local suppression at the gland site; small doses of androgen can overcome the sebum-suppressive effects of large doses of estrogen in women as well as in men. There is a direct correlation between the degree of sebaceous gland inhibition and acne improvement. The gland, however, responds variably to estrogen suppression. On average, there will be a decrease of 25% in sebum production on administration of 0.1 mg ethinyl estradiol. This drug and its 3-methyl ether, mestranol (which has two-thirds the potency of ethinyl estradiol), are the estrogens present in oral contraceptives. All combination birth control pills are antiandrogenic because they reduce free testosterone, testosterone conversion to 5- α -androstanediol, and sex hormone-binding globulin. With combination therapy, it is important to use a pill with adequate estrogenic effect linked with nonandrogenic progestones such as drospirenone, desogestrel, norgestimate, norethindrone, and ethynodiol diacetate. Drospirenone is a new progestogen with antimineralocorticoid, progestogenic, and antiandrogenic activity. Patients may exhibit a difference in the tolerability of side effects between the various progestational agents. If a patient has been taking an oral contraceptive with minimal side effects, the clinician does not need to change the pill unless there appears to be a correlation with worsening of acne.

The preferable pills are Yasmin (3 mg drospirenone and 0.03 mg ethinyl estradiol), Desogen and Ortho-Cept (0.15 mg desogestrel and 0.03 mg ethinyl estradiol), Ortho-Cyclen or Ortho Tri-Cyclen (0.25 mg norgestimate and 0.035 mg ethinyl estradiol), Alesse (0.1 mg levonorgestrel and 0.02 mg ethinyl estradiol), Ovcon 35 (0.4 mg norethindrone and 0.035 mg ethinyl estradiol), Brevicon (0.5 mg norethindrone and 0.35 mg ethinyl estradiol), Modicon (0.5 mg norethindrone and 0.035 mg ethinyl estradiol), and Demulen (0.05 mg ethinyl estradiol and 1.0 mg ethynodiol diacetate), in decreasing order of effectiveness.

Decrease in acne should be noted within 3 months and marked improvement should be noted within 4 months of administration. The progestational agents norgestrel and norethindrone acetate should be avoided (Ovral, Ovrette, Lo-Ovral, and Loestrin). Estrogen therapy is

rarely needed before age 16, after which time there will be no problem with growth retardation.

2. **Prednisone.** For individuals with an acute acne flare, prednisone can also be used in a dose of 20 mg/day for 1 week before an important occasion such as a wedding.
3. **Spironolactone (Aldactone),** used for many years as a diuretic, is also an antiandrogen that blocks the binding of androgens to androgen receptors. It is useful in treating recalcitrant acne in women with adult acne. Menstrual irregularities and breast tenderness are common side effects, and the drug may be easier to use in women taking birth control pills. The drug should not be used during pregnancy, because it may block the normal development of male genitalia. Most clinicians recommend combined use of this drug with oral contraceptives. Spironolactone alters potassium excretion (usually only at higher doses and in only 10% of patients). Serum electrolytes should be monitored during initial institution of therapy. Nausea, vomiting, and anorexia are also common side effects.

Good candidates for this drug are individuals with a premenstrual flare-up of their acne, acne onset after the age of 25, oily skin, coexistent hirsutism, and acne that has a predilection for the lower face, especially the chin and mandible. Start patients on 50 to 100 mg/day taken with meals. If no clinical response is seen in 1 to 3 months, adjust the dose up to 200 mg/day if necessary. Once maintenance has been achieved, try to lower the dose to the lowest effective daily dose. Keep in mind that hirsutism requires higher doses and longer treatment schedules.

4. **Isotretinoin (13-*cis*-Retinoic Acid, Accutane)** should be considered for patients with severe recalcitrant cystic acne, or patients with evidence of scar formation. The beneficial effects of this synthetic retinoid are indisputable, although its mode of action remains unclear. Isotretinoin is sebostatic, inducing a decrease in sebum production rates to as low as 10% of pretreatment values. However, given that sebum production approaches pretreatment rates after therapy is completed without a concomitant return of acne, other mechanisms, such as an anti-inflammatory effect and correction of altered keratinization, may be equally important. Isotretinoin therapy causes a 2.6-fold decrease in androgen site-binding capacity.⁴

The initial dose of isotretinoin is 0.5 to 1.0 mg/kg of the patient's body weight. The cumulative dose should be between 120 and 150 mg/kg, for optimal effectiveness and lasting results. This usually takes 5 to 6 months to achieve, depending on the daily dose the patient is able to tolerate. Although lower doses may achieve the same initial response rates, they are associated with a much higher recurrence rate on discontinuation of the drug.

In doses greater than 40 mg/day, the dose should be divided into morning and evening. Isotretinoin is fat soluble and absorption is enhanced by taking it with meals. Reports of treatment failure have been reported in patients taking concomitant anti-fat-absorbing medications or foods. Because the skin will often continue to clear after drug administration has been stopped, at least a 2-month waiting period and preferably a 6-month period is advised before one commits a patient to a second

course of therapy. Any woman who fails to respond to isotretinoin should be evaluated for hyperandrogenism. The response rate may be as high as 90% with one to two courses of treatment, and with adequate dosing, most patients experience prolonged remissions from their disease. In a 10-year follow-up study, 61% of patients were free from acne. Of those who relapsed, 23% required a second course. Ninety-six percent had relapsed within 3 years of therapy; truncal acne had a higher relapse rate.⁴

Intermittent isotretinoin at lower doses may benefit some patients with adult acne or stubborn isotretinoin treatment failures. In one study, with isotretinoin 0.5 mg/kg/day for 1 week every 4 weeks for a total of 6 months, the acne resolved in 88% of patients, and at 1 year, 39% had a relapse of their acne (73% relapse with truncal acne).⁴

Isotretinoin is teratogenic in humans. A pregnancy prevention program was initiated in 1988. Since that time, 0.3% of treated female patients have become pregnant; 38% of live born infants had retinoid embryopathic defects.

Women of childbearing age must have a negative pretreatment pregnancy test and continue adequate contraception for the duration of therapy. Because of the short half-life of isotretinoin, the current recommendation is that conception may be attempted 1 month after the cessation of treatment. Men may take isotretinoin without concern for its teratogenic effects. There has never been a report of retinoid embryopathic defects resulting from a man taking isotretinoin impregnating a female; however, patients are still advised not to take isotretinoin if they are actively trying to father a child. Both patients and physicians must register with the FDA-administered program iPLEDGE before starting the medication to minimize the risk associated with isotretinoin.

Other controversial and disputed associations include depression and IBD. The cases of depression may reflect an idiosyncratic response to the medication because larger, controlled studies have failed to find a causal association. Acne by itself can be associated with depression, but an increased awareness of this potential side effect of isotretinoin should be kept in mind before prescribing this drug and during follow-up. Recently, the association between IBD and isotretinoin has gained much attention from the media and has led to legal actions despite several studies suggesting no increased risk of IBD.^{5,6}

Xerosis, cheilitis, alopecia, dry eyes, muscle and bone aches, and hypertriglyceridemia are frequent side effects, but all are reversible on discontinuation of therapy. Although patients may experience a temporary flare-up of their acne when treatment is started, this does not affect their ultimate response to isotretinoin. Excessive granulation tissue, giving a pyogenic granuloma-like picture, is a less common problem. Because of delayed or poor wound healing, elective surgery including attempts at cosmetic scar revision should be delayed for 6 months after the completion of isotretinoin therapy. Patients should also be advised to avoid laser treatment, hair-removal waxing, tattoos, and piercing.

F. Adjunctive Therapy

1. **Intralesional Corticosteroids.** The therapy of choice for cystic lesions and acne abscesses is the intralesional injection of small amounts of corticosteroid preparations (triamcinolone acetonide or diacetate, 0.63 to

2.5 mg/mL). The high local concentration of corticosteroid injected leads to rapid involution of these nonpyogenic, sterile, inflammatory lesions. Use of undiluted solutions or injections of too large an amount may lead to temporary atrophic depressions in the skin. Most lesions, particularly early ones, will flatten and disappear within 48 hours of injection.

2. Acne Surgery

a. Comedo Expression. Gentle removal of comedones by pressing over the lesion with a comedo extractor not only relieves the patient of unsightly lesions but may also prevent progression to more inflammatory lesions. Occasionally, it may be necessary to incise the follicular opening carefully with a No. 11 scalpel blade or a 25-, 27-, or 30-gauge needle. Over-rigorous attempts to express comedones may result in an increased inflammatory response.

Recurrence of comedones after removal is common. Open comedones have been shown to recur within 24 to 40 days and closed comedones, within 30 to 50 days. Fewer than 10% of comedo extractions are a complete success. Nevertheless, this mode of therapy, carefully done, is useful in the appropriate case.

b. Draining of Cysts. Careful and judicious incision and drainage of cysts and/or abscesses may initiate healing and shorten the duration of lesions.

c. Microdermabrasion, with aluminum oxide crystals or other abrasive substances, is advocated for treatment of acne and acne scars. Early data indicate that this modality may be a useful adjunct to other topical therapies.

3. Laser and Light Therapies

a. Blue Light or Photodynamic Therapy (420 nm). These light sources cause an overproduction of porphyrins that are toxic to *P. acnes*. Pulsed green light (532 nm) is also approved for the treatment of acne and presumably works in the same way. Light treatments can be performed alone or with prior application of aminolevulinic acid 20% for 10 minutes to 2 hours. Protocols vary, but one standard treatment is every 3 weeks in a 3-month course. This may be performed in conjunction with other acne therapies.

b. Nonablative Lasers in the Infrared Range rely on selective photothermolysis to target the follicle. Through transient thermal effects, *P. acnes* is reduced and sebaceous glands are heated and decreased in size. The 1,320-nm Nd:YAG, 1,450-nm diode, and 1,540-nm Er:glass lasers may be of some benefit in the treatment of inflammatory acne and clinical improvement in acne scars. Treatments are typically performed monthly for 4 to 6 months. Other therapies may be continued concomitantly. The limiting factors are patient discomfort and expense.

c. Pulsed Dye Lasers in the Visible Light Range (585 to 595 nm) can be used to minimize erythema of active acne lesions and acne scars. However, data are inconsistent as to whether this laser decreases acne lesion counts.

d. Broadband Intense Light and Vacuum (Acleara System; Isolaz). The latest tool uses broadband light to activate porphyrins to destroy *P. acnes* and reduce sebum production, while a vacuum

removes built-up sebaceous material and extracts comedones. Visible improvement is often appreciated in two to three treatments at 2-week intervals. Maintenance therapy may be performed every 4 to 6 weeks pending the progress.

4. **α -Hydroxy Acids (Glycolic, Lactic, Pyruvic, and Citric Acids) and β -Hydroxy Acids (Salicylic Acid)** are available in topical cream formulations or as peeling agents. Peels are applied in the physician office. These acids reduce corneocyte cohesion.

G. Acne scars

1. **Laser Skin Resurfacing** with ablative lasers in various wavelengths can improve the appearance of acne scars of all types but requires significant postoperative wound care and recovery time. Fractional resurfacing devices allow for remodeling acne scars through a series of treatments with less downtime. Nonablative lasers (see preceding text) are thought to stimulate collagen production and, thereby, gradually improve the appearance of pitted acne scars.
2. **Dermabrasion Using High-Speed Diamond Buffing Drills** can remove small and superficial scars and sometimes deep scars. However, this method is highly dependent on practitioner technique and can result in scarring in untrained hands.
3. **Fillers.** Fat transfer and injection of dermal filler substances can be used to elevate acne scars.
4. **Surgical Techniques.** Punch excision, punch elevation, and elliptical excision can be used to remove isolated ice-pick or deep boxcar scars.

H. Patient Education about Long-Standing Misconceptions A number of myths circulate with regard to the relationship between habits, diet, hygiene, and acne. Patients should be counseled that if certain exposures aggravate their individual case of acne, these should be avoided. However, strict or fad diets and regimens are unlikely to affect sebaceous gland function or acne activity. Detailed information and instructions should be emphasized. Moreover, shared, realistic expectations between the physician and the patient of any acne treatment regimen or therapeutic approach are essential to achieve the desired improvement.

REFERENCES

1. Ramsay B, Alaghband-Zadeh J, Carter G, et al. Raised serum androgens and increased responsiveness to luteinizing hormone in men with acne vulgaris. *Acta Derm Venereol.* 1995;75:293-296.
2. Gough A, Chapman S, Wagstaff K, et al. Minocycline-induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome. *BMJ.* 1996;312:369-372.
3. Kapadia N, Talib A. Acne treated successfully with azithromycin. *Int J Dermatol.* 2004; 43:766-767.
4. Layton AM, Knaggs H, Taylor J, et al. Isotretinoin for acne vulgaris—10 years later: a safe and successful treatment. *Br J Dermatol.* 1993;129:292-296.
5. Bernstein CN, Nugent Z, Longobardi T, Blanchard JF. Isotretinoin is not associated with inflammatory bowel disease: a population-based case-control study. *Am J Gastroenterol.* 2009; 104:2774-2778.
6. Etminan M, Bird ST, Delaney JA, Bressler B, Brophy JM. Isotretinoin and risk for inflammatory bowel disease: a nested case-control study and meta-analysis of published and unpublished data. *JAMA Dermatol.* 2013;149(2):216-220.

I. BACKGROUND Alopecia areata (AA) is a common autoimmune disease of the hair follicle. The prevalence in the United States is 0.1% to 0.2%, with a lifetime risk of 1.7%. AA is characterized by rapid and often complete hair loss in one or more patches of skin. It most commonly affects the scalp (90% of cases), but may also involve the eyebrows, eyelashes, face, and other hair-bearing parts of the body (Figs. 2-1 and 2-2). The hair loss is non-scarring, and spontaneous remission occurs in 34% to 50% of patients within 1 year of disease onset.¹ While the exact etiology of AA remains unknown, evidence suggests that there is a T lymphocyte-mediated autoimmune reaction with antigens selectively expressed in the hair follicle. Environmental triggers have also been implicated in the pathogenesis.

AA appears to have a familial incidence of 10% to 30% and is highly associated with other disease processes. The most common of these comorbidities are autoimmune diseases, such as vitiligo, thyroid disease, diabetes mellitus, and rheumatoid arthritis, and atopic diseases, such as asthma, allergic rhinitis, and atopic dermatitis. There is also a significant association with Trisomy 21.

II. CLINICAL PRESENTATION AA most commonly affects the pediatric and young adult populations, but can occur at any age and has equal gender distribution. In most cases, there is rapid loss of hair in one or a few well-demarcated patches on the scalp. This is called *patchy AA*, which comprises 75% of cases. Active lesions are generally round or oval and are 1 to 5 cm in diameter with expanding margins characterized by “exclamation point” hairs—so called because the distal end of the hair shaft is of greater diameter than the proximal end. The skin at lesion sites usually shows no overt abnormalities, and there is complete preservation of the follicular ostia. Occasionally, lesions will show mild erythema and may be associated with pruritus and dysesthesia. However, the vast majority of cases are asymptomatic. In patients with lesions showing spontaneous remission, initial hair regrowth may appear as very fine vellus strands, which are often white. In approximately 10% of cases, patients will also develop uniform pitting of the nails in longitudinal or horizontal lines. Other acute nail involvement such as trachyonychia, periungual erythema, and red-spotted lunula may occur, but these are rare.

Aside from the more common *patchy* variant, AA may present as five other pattern subtypes:

- **Alopecia Reticularis:** Multiple lesions that may be either active, stable, or recovering simultaneously. A mosaic pattern is often observed.
- **Alopecia Totalis (AT; 10% to 20%):** Complete loss of scalp hair.
- **Alopecia Universalis (AU):** Complete loss of scalp and body hair (Fig. 2-3).
- **Diffuse AA:** Hair loss occurring in equal distribution throughout the scalp without the formation of discrete patches.
- **Ophiasis:** Band of hair loss along the occipital hairline that extends to the temples.



Figure 2-1. Alopecia areata. This child has smooth, well-demarcated, noninflammatory, asymptomatic patches of alopecia of the scalp. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 2-2. Alopecia areata. This man's alopecia is limited to his beard. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

III. WORKUP The diagnosis of AA can usually be made based solely upon patient history and clinical presentation. In cases of uncertainty, dermoscopy may be useful, which will reveal yellow dots indicating keratotic plugs within follicular ostia. If the diagnosis is still in question, a biopsy may be required



Figure 2-3. Alopecia universalis. This patient has lost most of her eye-brows, which she colors in with an eyebrow pencil. She also lacks eyelashes, pubic hair, axillary hair, and hair on her extremities. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

to rule out pathology that may mimic AA (Table 2-1). Histology will show peribulbar lymphocytic infiltrate (“swarm of bees”).

Because AA is associated with other autoimmune diseases, namely, thyroid disease, diabetes mellitus, and pernicious anemia, screening should be done at the time of diagnosis. Appropriate laboratory tests include TSH, free T4, fasting blood glucose levels, and CBC (Table 2-2). These tests are particularly important in the pediatric population, where there is a higher incidence of these comorbidities.

IV. TREATMENT No treatment has been shown to alter the disease course of AA. The goal of treatment is to suppress disease activity, rather than to cure or prevent it. It is also important to remember that treatment efficacy is highly dependent upon the extent and duration of disease and the age of disease onset

TABLE 2-1	Differential Diagnosis
<ul style="list-style-type: none">• Anagen effluvium• Androgenetic alopecia• Syphilitic alopecia• Systemic lupus erythematosus• Telogen effluvium• Tinea capitis• Traction alopecia• Trichotillomania	

TABLE 2-2 Laboratory Workup of Alopecia Areata

Biopsy
CBC
TSH
Free T4
Fasting glucose

(pediatric patients have the worse prognosis). Because most cases of AA will resolve spontaneously, reassurance and observation is a viable option for many patients. The cosmetic impact of the disease makes psychiatric comorbidities common, and patients should be directed to support groups to help cope if necessary. Table 2-3 summarizes the primary treatment options for AA.

A. Intralesional Corticosteroids Intralesional corticosteroid injections are the first line of therapy in adults. Regrowth may occur in up to 71% of patients using this modality. Treatment is less effective in pediatric patients and those with long-standing disease. Triamcinolone acetonide is the agent of choice, with concentrations typically ranging from 2.5 to 10 mg/mL. Recommended starting concentrations are 5 mg/mL for the scalp and 2.5 mg/mL for the face. A 3-mL syringe and 30-gauge needle is used to administer multiple 0.1 mL intradermal injections at 1 cm intervals at lesion sites. At a concentration of 5 mg/mL, a maximum of 3 mL should be administered during a single course of treatment. Injections are repeated every 4 to 6 weeks. If no improvement is observed after 6 months, treatment should be stopped as some AA patients exhibit glucocorticoid resistance.²

Side effects are minimal and may include telangiectasia and atrophy at injection sites. These may be minimized by injecting smaller volumes of agent and decreasing the number of injections per lesion site.

B. Topical Immunotherapy This modality is considered the treatment of choice for patients with greater than 50% scalp involvement. Topical immunotherapy induces contact allergy at application points on the skin. The current contact sensitizers in use are squaric acid dibutylester (SADBE) and diphencyprone (DPCP). Dinitrochlorobenzene (DNCB) is no longer used because of its carcinogenic potential. DPCP 2% should be applied initially to induce a 36-hour period of sensitization, which manifests as erythema and pruritus. Following sensitization, the lowest concentration that maintains this irritation should be applied on a weekly basis (typically 0.001%). Response to therapy is unpredictable. Success rate may reach

TABLE 2-3 Primary Treatment Options

1. Intralesional corticosteroids (triamcinolone acetonide)
2. Topical immunotherapy (DPCP, SADBE)
3. Topical steroids^a

^aFirst-line treatment in children <10 years of age only.

60%, with a reported relapse rate as high as 62%.³ In patients who fail to respond to DPCP, a trial of SADBE should be implemented. Topical immunotherapy is typically stopped if there is failure to respond within 6 months, although many physicians advocate continuing an extended course of therapy, given the unpredictable timing of response.

Side effects include pruritus and regional lymphadenopathy (cervical and occipital). While mild eczematous changes are expected, vesicular or bullous reactions occurring at treated areas are an indication to stop therapy. Rarely, an auto-sensitization reaction may develop that results in generalized eczema. Pigmentary changes may also occur at application sites, especially in darker skinned individuals.

C. Anthralin Anthralin is an irritant with an unknown mechanism of action.

It may suppress tumor necrosis factor- α , thereby acting as an immunosuppressant.⁴ Few studies have assessed the efficacy of this agent, and most show mixed results with a reported success rate of 25% to 75%. As a short contact therapy, anthralin 0.5% to 1% cream should initially be applied to affected areas daily for 30 minutes. Contact time should then be increased by 10 minutes every 2 weeks as tolerated, with the goal being a maximum contact time of 1 hour. Daily application at this established contact time is then continued for at least 3 months. Anthralin is only effective when it induces significant skin irritation, so it is important to apply the agent at a high enough concentration, frequency, and contact time. Adjustments to any of these three parameters should be made as needed. Combination therapy of 0.5% anthralin and 5% minoxidil has been shown to enhance response rate. Side effects may include folliculitis and lymphadenopathy. Dark staining of the skin also commonly occurs, which many dark-haired individuals perceive as cosmetically beneficial. Mild erythema and pruritus are expected.

D. Topical Steroids Topical corticosteroids are considered the treatment of choice in the pediatric population by many dermatologists. These agents have the benefit of low cost and convenience of use. In the entire AA patient population, however, study results have largely been mixed. Response rates are sometimes high in patchy AA, but are very low in AT and AU. Regimens include twice daily application for 3 months of either 0.1% betamethasone foam, 0.25% desoximetasone cream, or 0.05% clobetasol propionate ointment. There is evidence that application under occlusion may lead to improved outcomes. Side effects are minimal and include folliculitis and atrophy at application sites.

E. Minoxidil The mechanism of action for topical minoxidil is not entirely understood, but it may enhance regrowth through vasodilation, angiogenesis, and prolonged keratinocyte survival time. Response to treatment is highly dependent upon extent of disease: significant regrowth rates have been reported in patients with patchy AA, while there appears to be no effect in patients with AT or AU. Despite reports of success using this agent, most studies show that it rarely achieves regrowth of cosmetic value. Thus, it is best used as an *adjunctive* rather than a stand-alone therapy. Recommendations are twice daily application to affected sites with 5% solution, which is superior to the 1% formulation. Treatment should be continued for at least 3 months. Side effects include hypertrichosis and dermatitis. Irritation to the skin can be avoided by using 5% minoxidil foam, which does not contain a propylene glycol vehicle.

F. Camouflage Patients should be informed that there are alternatives to medical treatment. Many patients achieve cosmetically satisfying results with the use of acrylic or authentic hair wigs. There are also many concealer brands available that approximate real hair and are particularly effective in the patchy variant of AA. These include brands such as DermMatch and Toppik. Tattooing (dermatography) of the eyebrows is another option that will give patients good cosmetic results.

G. Other Treatments Because AA is so resistant to medical therapy, a vast number of treatments have been developed. Most of these modalities have not yet proven to be effective, and some may even be unsafe. The following are a list of treatments that should only be considered in AA cases refractory to the primary therapies discussed above:

- Topical psoralen plus ultraviolet A (PUVA)
- Excimer laser
- Sulfasalazine
- Prostaglandin analogs
- Biologic therapy (infliximab and adalimumab)
- Topical tacrolimus

While studies have shown some success with high doses of pulsed systemic corticosteroids, they should not be used, given their high rate of relapse and exceedingly toxic drug profile for prolonged administration.

REFERENCES

1. Szu-Ying C, Yi-Ju C, Tseng WC, et al. Comorbidity profiles among patients with alopecia areata: the importance of onset age, a nationwide population-based study. *J Am Acad Dermatol.* 2011;65(5):949-956.
2. Sohn KC, Jang S, Choi DK, et al. Effect of thioredoxin reductase 1 on glucocorticoid receptor activity in human outer root sheath cells. *Biochem Biophys Res Commun.* 2007;356:810-815.
3. Wiseman MC, Shapiro J, MacDonald N, Lui H. Predictive model for immunotherapy for alopecia areata with diphencyprone. *Arch Dermatol.* 2001;137:1063-1068.
4. Tang L, Cao L, Sundberg JP, Lui H, Shapiro J. Restoration of hair growth in mice with an alopecia areata-like disease using topical anthralin. *Exp Dermatol.* 2004;13:5-10.

SUGGESTED READINGS

- Alkhalifah A, Alsantali A, Wang E, McElwee KJ, Shapiro J. Alopecia areata update: part I. Clinical picture, histopathology, and pathogenesis. *J Am Acad Dermatol.* 2010; 62(2):177-188.
- Finner AM. Alopecia areata: clinical presentation, diagnosis, and unusual cases. *Dermatol Ther.* 2011;24(3):348-354.

I. BACKGROUND Androgenetic alopecia (ADA) is the most common form of hair loss. By age 70, approximately 80% of Caucasian men and 50% of women will have ADA, also referred to as male pattern hair loss (MPHL) and female pattern hair loss (FPHL).^{1,2} The etiology of ADA is multifactorial, with features such as genetic predisposition and alterations in androgen metabolism playing major roles in its development.^{2,3} ADA is characterized by shortening of the anagen phase, or active growth phase, of the hair growth cycle. In addition, individual follicles undergo progressive miniaturization, replacing long terminal hairs with vellus-like hairs (Fig. 3-1). This process results in clinically apparent thinning of hair. Overt baldness, however, is only seen after all follicles contained within a follicular unit have undergone miniaturization.⁴

Androgen hormones, in particular dihydrotestosterone (DHT), play a critical role in the pathogenesis of MPHL. Testosterone is converted to the active metabolite DHT by the enzyme 5α -reductase, which has two isoenzymes (types I and II). Type 1 5α -reductase is largely found in sebaceous glands, while type II 5α -reductase is present in high concentrations in the inner root sheaths of hair follicles and in the prostate gland. Men with androgenetic hair loss have increased amounts of DHT and 5α -reductase in scalp follicles, and men lacking 5α -reductase do not develop MPHL.^{2,5} Additionally, 5α -reductase inhibitors are efficacious in treating male pattern baldness.⁵ In contrast, the role of androgens in FPHL is less clear. Although FPHL often occurs in women with hyperandrogenism, the majority of women with FPHL have normal androgen levels.⁶ Female hair loss patients have less distinct patterns of alopecia and increased frequency of confounding factors, such as anemia, autoimmune disease, pregnancy, and the use of topical hair products. Additionally, treatment with 5α -reductase inhibitors has a less consistent success rate in FPHL than in MPHL.^{7,8}

II. CLINICAL PRESENTATION Men and women typically present with gradual, symmetric thinning of hair in a distinct pattern. This process begins postpubertally, and the incidence increases with advancing age. The amount of hair shedding and the time course may vary substantially from individual to individual.⁷ Men typically develop frontoparietal and frontal recession as well as vertex thinning, sometimes referred to as “M” pattern alopecia (Fig. 3-2). Progression of MPHL is commonly classified on the Hamilton-Norwood scale, ranging from stages I to VII based on the extent of alopecia.² Women usually have diffuse central thinning of the crown and frontal scalp, described as a “Christmas tree” pattern.² The frontal hairline is variably preserved in women (Fig. 3-3).^{2,7} The Ludwig (three-point) classification grades the degree of alopecia on frontal and vertex scalp, with relative preservation of the frontal hairline.⁷ Occasionally, female patients present with “male-type” frontotemporal and vertex thinning.

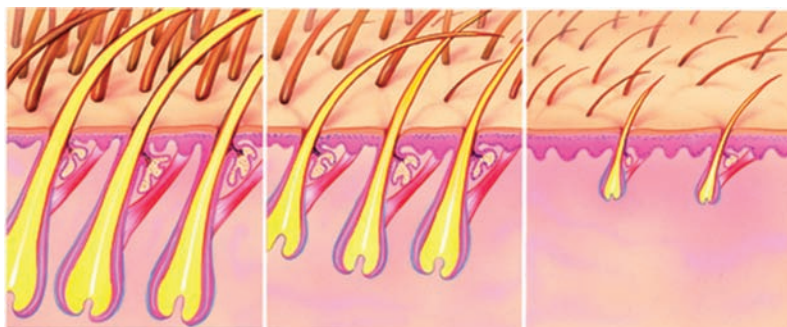


Figure 3-1. Miniaturization of hair follicles in androgenetic alopecia. (With permission from Anatomical Chart Co.)



Figure 3-2. Male pattern baldness is characterized by an M-shaped pattern of hair loss on the front and vertex of the head. (With permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

III. WORKUP ADA is predominantly a clinical diagnosis, with typical history and hair loss patterns. Clinical evaluation should include examination of the scalp skin, hair density, and extent of facial and body hair. In female patients, one should also pay particular attention to signs of hyperandrogenism (e.g., acne and hirsutism).⁷ Laboratory examination is based upon appropriate history and physical findings (Table 3-1). Male patients seldom require laboratory evaluation.



Figure 3-3. Female pattern baldness occurs in a “Christmas tree” midparietal pattern of decreasing hair loss toward the vertex (the “widened part”). The integrity of the frontal hairline is maintained. (With permission from Goodheart HP. *Goodheart’s Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

Scalp biopsy may be helpful to rule out processes that may clinically mimic ADA, such as chronic telogen effluvium, diffuse alopecia areata, and hypothyroidism. Histology displays normal total number of follicles, no significant inflammation, and increased percentage of vellus hairs, and may exhibit perifollicular fibrosis. Terminal hairs are characterized by hair shafts >0.03 mm in diameter and thicker than the follicle’s inner root sheath. Miniaturized hairs have hair shafts ≤ 0.03 mm in diameter and thinner than the follicle’s inner

TABLE 3-1	Summary of Laboratory Evaluation
Laboratory Test	Recommended for
Serum ferritin \pm serum iron and total iron-binding capacity	Females. Select male patients, especially if following strictly vegetarian or otherwise deficient diet
Complete blood cell count and/or free thyroxine	Patients with pertinent historical positives/symptoms
Free and/or total testosterone \pm dehydroepiandrosterone sulfate and 17-hydroxy-progesterone	Women with concomitant signs/symptoms of hyperandrogenism (hirsutism, adult acne, acanthosis nigricans, irregular menses, and/or galactorrhea)
Prolactin	Women with galactorrhea or increased testosterone

root sheath.² While the normal ratio of terminal to vellus hair is 7:1, in ADA, the ratio decreases to approximately 2:1.² Additionally, telogen hairs typically increase from a normal of 5% to 10% to 15% to 20%.² The hair pull test, hand-held epiluminescent microscopy, and phototrichography may further analyze hair caliber, density, and growth rate.⁶

IV. TREATMENT Although progressive hair loss may seem a natural, commonplace occurrence, regression of hair can have a profound impact on an individual's sense of self-esteem and identity. Treatment must be determined on a case-by-case basis balancing clinical benefits with potential medication side effects and health risks. This is especially relevant in FPHL, where, apart from topical minoxidil, most treatments have not been evaluated in well-designed, randomized controlled trials.⁷ The most common treatment options for MPHL and FPHL are summarized in Table 3-2.

- A. Minoxidil (Topical 1%, 2%, and 5% Formulations)** is a piperidinopyrimidine derivative and potent vasodilator that possesses hair growth stimulant properties, converting vellus to terminal hairs. Minoxidil enhances proliferation and differentiation of follicular keratinocytes, which prolongs the anagen phase; however, the exact mechanism of action of hair growth stimulation is unknown.^{2,7} In the early phase of treatment, shedding of telogen hairs can lead to a paradoxical worsening of alopecia approximately 4 to 6 weeks following treatment initiation.² Patients should be counseled to continue treatment through this period, as this effect subsequently resolves. Hair regrowth is greatest on frontal and vertex scalp, but somewhat recalcitrant on the bitemporal areas. Twice-daily treatment application of 5% formulation is the most efficacious regimen for male patients; there are insufficient data to recommend this dose in female patients.⁸ Currently, only the 2% formulation is US Food and Drug Administration (FDA) approved for use in women. It is contraindicated in pregnant and lactating women. Adverse reactions, which are relatively minimal, include local irritation, contact dermatitis, and reversible facial hypertrichosis.^{7,8} These effects are more commonly seen in women using 5% solution twice daily. With treatment cessation, clinical regression of regrowth occurs. **Aminexil** is a derivative of minoxidil with a similar mode of action. It is available in shampoos, but has not been approved by the FDA or the European Medicines Agency (EMA).⁷
- B. Spironolactone (Aldactone)**, a synthetic steroid diuretic that resembles aldosterone, directly blocks the binding of androgens to androgen receptors, reduces the activity of 5 α -reductase, and inhibits the biosynthesis

TABLE 3-2 Primary Treatment Options

Male Patients	Female Patients
Minoxidil 5%	Minoxidil 2%
Finasteride	Antiandrogen products (spironolactone/hormonal contraception)
Surgery	Surgery

of androgens. It is a commonly prescribed medication in the United States for FPHL. Dosage ranges from 50 to 200 mg/day. Contraception is necessary in women of childbearing age due to the risk of feminization of a male fetus, and most clinicians recommend combined use of this drug with oral contraceptives.⁹ Side effects include hypotension, electrolyte imbalance, nausea, vomiting, anorexia, menstrual irregularities, fatigue, urticaria, and breast tenderness.⁷ Prior to initiating therapy, it is important to exclude pre-existing hyperkalemia or impaired renal function. Some physicians monitor blood pressure and serum electrolytes during commencement of therapy. It is uncommon, however, to experience hyperkalemia from spironolactone in healthy individuals.⁹ Spironolactone is also useful for other androgen-responsive disorders such as hirsutism and acne. It is poorly tolerated in men owing to adverse endocrine side effects.

- C. Finasteride (Propecia)** is a synthetic 4-azasteroid compound that competitively inhibits type II 5 α -reductase, thus blocking the peripheral conversion of testosterone to DHT. Finasteride has been effective in promoting hair growth in adult men with mild-to-moderate ADA. It is most effective for vertex and mid-scalp loss. Its effectiveness has not been investigated for bitemporal loss. Dosing ranges from 1 to 5 mg daily for adult male patients with mild-to-moderate ADA. New hair growth appears as early as 6 months into treatment, but may not be clinically evident until 12 months after treatment initiation.⁸ Continual usage is necessary to sustain hair regrowth, and benefits are lost after stopping treatment. Postmenopausal women may respond to higher daily doses of finasteride, but high-quality, controlled clinical trials are still required to better assess its efficacy.⁸ Finasteride is contraindicated in pregnant women and children, as decreased DHT production may result in feminization of developing male genitalia. Other side effects are rare; less than 2% of men report sexual dysfunction, and women may experience breast tenderness and increased libido.⁷ Because finasteride lowers the levels of serum prostate-specific antigen (PSA), the clinician should suspect a falsely low PSA level when screening for prostate cancer.^{2,5,8} A baseline PSA should be obtained in males over 40 or those with a family history of prostate cancer prior to initiating finasteride.
- D. Dutasteride (Avodart)** is a combined type I and type II 5 α -reductase inhibitor currently FDA approved for the treatment of benign prostatic hyperplasia. It has been shown to lead to a greater reduction in serum and scalp DHT levels than finasteride.⁷ A phase III trial showed that 0.5 mg/day was more effective than placebo for hair regrowth for adult men with mild-to-moderate ADA.¹⁰ The potential for teratogenicity and prolonged biologic half-life prohibit its use in women of childbearing age.
- E. Cyproterone Acetate (Topical and Oral Forms; Available in Europe and Canada Only)** is a progestin, which blocks androgen receptors and suppresses luteinizing hormone. It is often prescribed in a combination with oral contraceptives to be taken on days 5 to 15 of the menstrual cycle. Side effects include depression, weight gain, breast tenderness, and loss of libido.⁷
- F. Flutamide (Eulexin)** is an androgen receptor blocker that has been used for the treatment of ADA. However, the risks of severe hepatotoxic effects and lipid abnormalities make this an expensive, high-risk therapy that is typically used only in recalcitrant cases.⁷

TABLE 3-3 **Alternative Therapies**

Aloe vera	Hibiscus
Aminexil	Iron supplements in the absence of iron deficiency
Amino acids	Ketoconazole
β -Sitosterol	Low-level laser
Bergamot	Marine extract and silicea component
Botulinum toxin	Melatonin
Caffeine	Mesotherapy
<i>Cimicifuga racemosa</i>	Millet seed
Corticosteroids	Polysorbate 60
Cyclosporine	Proanthocyanidins
Electromagnetic/-static field	Prostaglandins (viprostol, latanoprost)
<i>Ginkgo biloba</i>	Retinoids
<i>Ginseng</i>	Saw palmetto
Glyceroloxiesters/silicium	Sorophora
Green tea	Vitamins/minerals (biotin, niacin derivatives, zinc, copper)

G. Surgical Hair Replacement options include follicular unit transplantation and scalp reduction in appropriate surgical candidates. For transplantation, patients must have a sufficient amount of donor hair, which is usually harvested from the relatively preserved posterior scalp. The technique is performed in an outpatient setting under local anesthesia. Grafts heal within 24 hours, and new growth occurs over the next 6 to 8 months.⁵ Patients should continue other oral and topical treatments for enhanced outcome.⁸

H. Alternative Therapies have been widely marketed to improve ADA. These include food and herbal supplements, laser therapy, and less frequently used medications, such as cimetidine and ketoconazole (Table 3-3). However, at this time, there are an insufficient number of clinical trials to determine the effectiveness of these treatments.⁸ Cosmetic products are also valuable management options. These include hairstyling techniques, hairpieces, camouflage products, and hair accessories.

REFERENCES

1. Severi G, Sinclair R, Hopper JL, et al. Androgenetic alopecia in men aged 40–69 years: prevalence and risk factors. *Br J Dermatol*. 2003;149:1207-1213.
2. Olsen EA, Messenger AG, Shapiro J, et al. Evaluation and treatment of male and female pattern hair loss. *J Am Acad Dermatol*. 2005;52(2):301-311.

3. Drake LA, Dinehart SM, Farmer ER, et al. Guidelines of care for androgenetic alopecia. American Academy of Dermatology. *J Am Acad Dermatol.* 1996;35(3 Pt 1):465-469.
4. Yazdabadi A, Magee J, Harrison S, Sinclair R. The Ludwig pattern of androgenetic alopecia is due to a hierarchy of androgen sensitivity within follicular units that leads to selective miniaturization and a reduction in the number of terminal hairs per follicular unit. *Br J Dermatol.* 2008;159:1300-1302.
5. van Zuuren EJ, Fedorowicz Z, Carter B, Andriolo RB, Schoones J. Interventions for female pattern hair loss. *Cochrane Database Syst Rev.* 2012;5:CD007628.
6. Blumeyer A, Tosti A, Messenger A, et al. European Dermatology Forum (EDF). Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and in men. *J Dtsch Dermatol Ges.* 2011;9(Suppl 6):S1-S57. doi:10.1111/j.1610-0379.2011.07802.x.
7. Rogers NE, Avram MR. Medical treatments for male and female pattern hair loss. *J Am Acad Dermatol.* 2008;59(4):547-566; quiz 567-568.
8. Sinclair R, Patel M, Dawson TL Jr, et al. Hair loss in women: medical and cosmetic approaches to increase scalp hair fullness. *Br J Dermatol.* 2011;165(Suppl 3):12-18. doi:10.1111/j.1365-2133.2011.10630.x.
9. Kim GK, Del Rosso JQ. Oral spironolactone in post-teenage female patients with acne vulgaris: practical considerations for the clinician based on current data and clinical experience. *J Clin Aesthet Dermatol.* 2012;5(3):37-50.
10. Eun HC, Kwon OS, Yeon JH, et al. Efficacy, safety, and tolerability of dutasteride 0.5 mg once daily in male patients with male pattern hair loss: a randomized, double-blind, placebo-controlled, phase III study. *J Am Acad Dermatol.* 2010;63(2):252-258. Epub 2010 Jun 3.

4

Aphthous Stomatitis (Canker Sores)

Michelle T. Chevalier and David C. Reid

I. BACKGROUND Aphthous stomatitis is a common inflammatory condition characterized by clinically characteristic ulcerations of the oral mucosa. The associated pain may be severe, leading the patient to experience difficulty with eating and speaking. Ulceration typically occurs in a periodic fashion, which has led to the frequent use of the term *recurrent aphthous stomatitis* (RAS). The lifetime incidence of this disease is estimated at 20%, with a slight female predominance. The peak age of onset occurs in the second decade, with a higher prevalence and disease severity seen in children of higher socioeconomic status. With age, the frequency of recurrences and overall disease severity tend to diminish. While the etiology remains largely unknown, it is thought to involve a complex interplay between genetic predisposition, environmental factors, and immune dysregulation. Although conflicting data exist and anecdotal claims are rarely substantiated with controlled studies, several factors have been reported to precipitate disease expression in some individuals (Table 4-1).

The classification of RAS includes an assessment of lesion morphology, severity, and systemic involvement. The three morphologic variants include minor, major, and herpetiform aphthae. The designation of simple aphthosis applies to cases with a limited frequency of recurrence (~2 to 4 episodes per year) and no associated systemic findings. In contrast, complex aphthosis features genital involvement, continuous disease activity, and/or systemic symptoms. Systemic disease entities that may present with aphthous-like lesions include Behçet's disease, reactive arthritis, gastrointestinal diseases (e.g., gluten-sensitivity enteropathy, inflammatory bowel disease), PFAPA syndrome, MAGIC syndrome, Sweet syndrome, and immunodepressed states [e.g., HIV (human immunodeficiency virus) infection, leukemia, and cyclic neutropenia] (Table 4-2). Of note, the oral ulcers of Behçet's disease may precede systemic involvement for 7 to 8 years. Several medications have been implicated in producing aphthous-like lesions, including nonsteroidal anti-inflammatory drugs, activator of ATP-sensitive potassium (nicorandil), angiotensin-converting enzyme inhibitors, β -blockers, and alendronate.

II. CLINICAL PRESENTATION All varieties of aphthae are painful and prone to recurrence. They may present as solitary or multiple lesions. In one individual, a combination of aphthae variants may occur over the course of their disease. The recurrent aphthous-like lesions seen in the setting of systemic disease may be indistinguishable from those of the primary type. Nearly all patients (99%) with Behçet's disease present with oral lesions, which tend to follow a more severe course than idiopathic aphthae, but otherwise display no distinguishable clinical features.

TABLE 4-1 **Precipitating Factors Reported for Recurrent Aphthous Stomatitis**

Precipitating Factors	Description
Hormonal fluctuation	A minority of women display cyclical ulceration related to their menstrual cycle; complete remission has been reported during pregnancy
Food hypersensitivity	Certain foods (e.g., cow's milk, gluten, chocolate, nuts, cheese, azo dyes, flavoring agents, and preservatives) have been associated with flaring
Hematologic deficiencies	Iron, folate, and vitamin B ₁ , B ₂ , B ₆ , and B ₁₂ deficiencies have been reported
Zinc deficiency	Improvement has been noted in some patients following zinc sulfate supplementation
Local trauma	Trauma related to anesthetic injections, sharp-edged foods, tooth-brushing, and dental treatments may trigger flaring
Tobacco withdrawal	Smoking seems to provide a protective effect, with smokers less often affected than nonsmokers. Smoking cessation may lead to flaring
Stress	Anxiety, depression, job-related stress, and other psychological states may be associated with ulcer recurrence

Minor aphthae are the most common variant, comprising ~80% of all cases. They present as small (<10 mm diameter), round- or oval-shaped, shallow ulcers. In well-developed lesions, a gray-white pseudomembrane and surrounding erythematous halo may be seen (Fig. 4-1). Nonkeratinizing mucosa (e.g., labial mucosa, buccal mucosa, and floor of the mouth) is most commonly involved; minor aphthae only rarely occur on keratinized sites (e.g., palate and dorsal tongue). They may occur at any frequency and heal without scarring in 10 to 14 days.

Major aphthae (peradenitis mucosa necrotica recurrens or Sutton disease) occur far less frequently (~10% of cases). Their clinical appearance differs from that of minor aphthae in that they are larger (>10 mm diameter), are deeper, and have a higher propensity to involve keratinizing sites (Fig. 4-2). They may persist for over 6 weeks and often heal with scarring. If a single lesion is longstanding and recalcitrant to treatment, the possibility of malignancy must be considered.

Herpetiform aphthae are the least common variant and most closely resemble ulceration secondary to herpes simplex infection. Herpetiform aphthae typically present as widely distributed, small (2 to 3 mm) ulcerations in the oral cavity. They often can be found to coalesce into large, irregularly shaped ulcers. They heal relatively quickly (7 to 10 days) and usually heal without scarring. This type often appears later in onset than the minor and major variants, and

TABLE 4-2 Diseases with Aphthous-Like Lesions

Disease	Diagnostic Features
Behçet's disease	International Study Group criteria for diagnosis: Recurrent oral ulceration (≥ 3 per year) in addition to two of the following features: Recurrent genital ulceration, ocular inflammation, defined skin lesions (erythema nodosum, skin pustules, etc.), and positive pathergy test.
Reactive arthritis	Typical triad of uveitis, conjunctivitis, and HLA B27-positive arthritis. Follows nongonococcal urethritis or bacillary dysentery.
Gluten-sensitive enteropathy (celiac disease)	Gastrointestinal intolerance to gluten protein of wheat products. May be associated with cutaneous findings of dermatitis herpetiformis.
Inflammatory bowel disease	Associated with both Crohn disease and ulcerative colitis.
PFAPA syndrome (Marshall syndrome)	Periodic fever, aphthae, pharyngitis, and adenitis.
MAGIC syndrome	Mouth and genital ulcers with inflamed cartilage. Has features of both Behçet's disease and relapsing polychondritis.
Sweet syndrome (acute febrile neutrophilic dermatosis)	Fever, neutrophilia, and tender erythematous skin lesions. Often associated with malignancy, most commonly acute myelogenous leukemia.
HIV infection	Prevalence rate of 1–4% for HIV-infected patients. Often with more severe involvement which may correlate with degree of immunosuppression. Esophageal and more distal gastrointestinal involvement has been reported.
Leukemias	May be suggested by repeat infections, anemia, or skin findings of petechiae and/or purpura
Cyclic neutropenia	Ulcers recur on a regular 3-wk cycle in association with neutropenia.
Drug-related	Discontinuation of drug coincides with remission.

HIV, human immunodeficiency virus.



Figure 4-1. Minor aphthae. (Neville BW, Damm DD, White DK. *Color Atlas of Clinical Oral Pathology*. 2nd ed. Baltimore, MD: Williams & Wilkins; 1998; Figure 6.2.)



Figure 4-2. Major aphthae; patient with Behçet's disease. (Neville BW, Damm DD, White DK. *Color Atlas of Clinical Oral Pathology*. 2nd ed. Baltimore, MD: Williams & Wilkins; 1998; Figure 6.6.)

occurs more commonly in women. In contrast to herpes simplex virus–related ulcers, herpetiform aphthae do not start as a vesicle.

III. WORKUP Given the minor severity of disease, patients with simple aphthosis rarely present to the physician and, when they do, generally do not require further evaluation. In cases of complex aphthosis or abrupt onset of

aphthae in an adult, clues for an underlying disease process should be sought. A full history, dermatologic examination, and appropriate laboratory studies are warranted. A thorough review of symptoms should be completed to identify any potential systemic involvement. Skin examination should include a detailed assessment of the oral and genital mucosa, as well as close inspection for the presence of other skin findings which may suggest an underlying disease process (Table 4-1).

Laboratory testing may include a complete blood count to assess for the possibility of an underlying leukemia or other blood dyscrasia. HIV testing should be considered in patients with risk factors for infection. Testing of ferritin, folate, and B vitamin levels may also be considered. In cases of Behçet's disease, inflammatory markers will be nonspecifically elevated. In the setting of aphthous ulceration without detectable systemic involvement, HLA-B51 testing does not reliably predict a patient's future risk of developing Behçet's disease.

Allergy testing may be warranted in selected cases where food seems to be an inciting factor. If a diagnosis of gluten-sensitive enteropathy is considered, serologic testing for antigliadin and transglutaminase antibodies as well as a referral for a small intestinal biopsy may prove helpful. Any lesion suspicious for malignancy or lacking a clear diagnosis should be biopsied. In cases where the possibility of herpes infection is considered, appropriate virologic studies are indicated (Table 4-3).

IV. TREATMENT The treatment goals for aphthous stomatitis include decreasing pain, reducing lesion duration, and minimizing recurrence. Any predisposing factors, such as vitamin or iron deficiencies, should be addressed at the onset of treatment to optimize outcomes. Patients should be advised to avoid spicy, salty, and acidic foods. The consumption of alcoholic beverages and food with sharp edges should also be discouraged. The maintenance of oral hygiene is crucial, but should be done with minimal trauma. Irritating products such as toothpastes containing sodium lauryl sulfate should be avoided. The therapeutic ladder typically begins with topical agents, with progression to systemic treatment only in severe and frequently recurrent cases (Table 4-4).

A. Locally Administered Agents. Topical agents are the first-line treatment for RAS. Comparison studies of these products used alone or in combination are limited and no single agent has been found to be superior. In order to maximize therapeutic outcome, ulcer sites should be gently dabbed dry before the use of topical agents. Following application, the

TABLE 4-3 Differential Diagnosis

- Herpes infection
- Autoimmune bullous disease
- Fixed drug eruption
- Stevens-Johnson syndrome
- Erosive lichen planus
- Mucosal malignancy

TABLE 4-4	Primary Treatment Options
Topical Agents	Systemic Agents
Topical corticosteroids	Oral corticosteroids
Antibacterial mouthwash	Colchicine
Amlexanox 5% paste	Dapsone

patient should avoid eating or drinking for at least 30 minutes. Given the limited contact time of medications in the oral cavity, treatments must often be repeated up to four times daily.

- 1. Corticosteroids.** Corticosteroid agents may be applied in several different topical vehicles. Most patients prefer a gel- or paste-based product. Triamcinolone Orabase 0.1% paste is Food and Drug Administration (FDA) approved for any inflammatory condition of the mouth. Other possible treatments include more potent topical steroids (e.g., fluocinonide and clobetasol) in a gel or ointment base. Some authors have advocated the use of hydrocortisone 2.5% lozenges. Steroids may be used in a rinse form when ulcers cover a large area, or when the patient is unable to directly apply topical agents. Oropharyngeal ulcers have also been treated with corticosteroid inhalers (without inhalation). Intralesional steroid injection may be attempted at the base of recalcitrant lesions. Side effects of long-term use of any locally administered steroid agent includes mucosal atrophy and an increased risk of local fungal (i.e., thrush), viral, and bacterial infection. An increased absorption potential at mucosal sites must also be considered.
- 2. Antimicrobial Agents.** Tetracycline 5% mouthwash can be used to reduce the pain and duration of aphthous ulcers. Aside from its antibacterial action, it is thought to inhibit collagenase activity and have an immunomodulatory effect. Potential adverse effects include teeth staining (if child swallows), dysgeusia, fungal overgrowth, mucocutaneous reactions, and fetal harm. Other antimicrobial mouthwashes that may be considered include Listerine, chlorhexidine gluconate, and triclosan. If chlorhexidine gluconate mouthwash is prescribed, the patient must be warned of its bitter taste and reversible brown staining of the teeth and tongue.
- 3. Amlexanox 5% Paste.** This is an anti-inflammatory agent compounded in an adhesive base. It carries FDA approval for aphthous ulcers.
- 4. Anesthetics.** Anesthetic agents such as lidocaine (5%) gel or viscous xylocaine may be used for temporary relief of ulcer pain. These agents may cause local numbness and stinging, and may rarely incite a hypersensitivity reaction.
- 5. Protective Bioadhesives.** Dental products containing carmellose (Orabase) or cyanoacrylate may be used as a barrier against trauma and may help reduce pain. Some patients may have religious objection to the use of gelatin found in carmellose. Sucralfate is a water-insoluble salt

preparation, commonly used to treat peptic ulcers. It works by adhering to the ulcer site, with the formation of a protective barrier.

6. **Topical Immunomodulators.** Topical tacrolimus and pimecrolimus have been utilized in the treatment of aphthous ulcers. The black-box warning on these products should be discussed with the patient prior to use.
7. **Others.** 5-Aminosalicylic acid 5% cream or toothpastes containing amyloglucosidase and glucose oxidase can be used to reduce pain and the duration of oral aphthae. Remission of aphthosis during therapy with chewable nicotine tablets has also been reported.

B. Systemic Medications. Systemic agents that have been used most commonly in the treatment of severe cases of RAS include oral corticosteroids, colchicine, dapsone, pentoxifylline, and thalidomide. Although treatment success has been reported for these agents, robust randomized clinical trials are lacking. One therapeutic ladder of systemic agents that has been proposed includes a step-wise trial of colchicine → dapsone → dapsone + colchicine → thalidomide, all in conjunction with topical therapy (Letsinger, McCarty, and Jorizzo). Other less commonly used medications include irsogladine maleate (type 4 phosphodiesterase), antimetabolites (azathioprine and methotrexate), calcineurin inhibitors (cyclosporine), alkylating agents (chlorambucil and cyclophosphamide), interferon- α , and biologics (infliximab and etanercept). Physician experience with the use of these agents is paramount, as appropriate monitoring of systemic effects is important for patient safety.

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Suggested Readings

- Altenburg A, Abdel-Naser MB, Seeber H, et al. Practical aspects of management of recurrent aphthous stomatitis. *JEADV*. 2007;21:1019-1026.
- Baccaglini L, Lalla RV, Bruce AJ, et al. Urban legends: recurrent aphthous stomatitis. *Oral Dis*. 2011;17:755-770.
- Chattopadhyay A, Shetty KV. Recurrent aphthous stomatitis. *Otolaryngol Clin N Am*. 2011;44:79-88.
- Femiano F, Lanza A, Buonaiuti C, et al. Guidelines for diagnosis and management of aphthous stomatitis. *Pediatr Infect Dis J*. 2007;26:728-732.
- Letsinger JA, McCarty MA, Jorizzo JL, et al. Complex aphthosis: a large case series with evaluation algorithm and therapeutic ladder from topicals to thalidomide. *J Am Acad Dermatol*. 2005;52:500-508.
- Natah SS, Kontinen YT, Enattah NS. Recurrent aphthous ulcers today: a review of the growing knowledge. *Int J Oral Maxillofac Surg*. 2004;33:221-234.
- Scully C. Aphthous ulceration. *N Engl J Med*. 2006;355:165-172.

5

Bacterial Skin Infections

Nilanthi Gunawardane

Bacterial skin infections are a common cause for visits to a health-care provider. Superficial bacterial skin infections are usually caused by staphylococci or streptococci. Risk factors for bacterial skin infections include antecedent cutaneous lesions, obesity, malnutrition, diabetes, and acquired or inherited immune dysfunction (Table 5-1).

IMPETIGO

I. BACKGROUND Impetigo is caused primarily by *Staphylococcus aureus*. Other causes include group A *Streptococcus* or a combination of *S. aureus* and group A *Streptococcus*. Impetigo is contagious and can easily be spread through person-to-person contact or through fomites. Predisposing factors include poor health and hygiene, malnutrition, and warm climate, as well as antecedent scabies, chickenpox, contact and atopic dermatitis, and other eruptions causing skin breakdown. Postinfectious acute glomerulonephritis is quite rare in the United States (up to 5% of patients with impetigo). Nephritogenic strains of *Streptococcus* include serotypes 1, 4, 12, 25, and 49.

Bullous staphylococcal impetigo is seen primarily in children. It is caused by group II phage types 70 and 71 staphylococci and rarely by group A *Streptococcus*. These organisms elaborate an exfoliative toxin that induces a split at the granular layer of the epidermis, resulting in blister formation. This toxin may also cause an exfoliative dermatitis (Ritter disease, staphylococcal scalded-skin syndrome) in infants and children.

II. CLINICAL PRESENTATION Impetigo is common in children and is usually located on the face and other exposed areas. Perinasal or perioral lesions may follow an upper respiratory tract infection. Impetigo begins as a small erythematous macule that rapidly develops into a fragile vesicle with an erythematous areola. The vesicopustule breaks and leaves red, oozing erosion capped with a thick, golden yellow crust (Fig. 5-1). Satellite lesions are often seen. Impetigo can be either asymptomatic or pruritic. Regional lymphadenopathy and elevated white blood cell count may be present and extensive impetigo may be seen in immunocompromised patients. Infants have a predilection for impetigo in the inguinal folds and diaper area, which may later generalize.

The presenting lesions of bullous staphylococcal impetigo are flaccid bullae that are first filled with clear, then cloudy, fluid which are replaced after rupture by a thin, varnish-like crust. Lesions may be up to 1 cm or more in diameter and may lack surrounding erythema.

TABLE 5-1 Treatment of Bacterial Skin Infections

Skin Infection	Treatment
Impetigo	<ol style="list-style-type: none"> Topical antibiotics: mupirocin, fusidic acid, and retapamulin Systemic antibiotics: penicillinase-resistant penicillins, cephalosporins, and macrolides Wound care: warm water or saline soaks
Folliculitis	<ol style="list-style-type: none"> Topical antibiotics: clindamycin, mupirocin, and antibacterial soaps Systemic antibiotics: penicillinase-resistant penicillins, cephalosporins, and macrolides Isotretinoin for gram-negative folliculitis
Cellulitis	<ol style="list-style-type: none"> Systemic antibiotics: penicillinase-resistant penicillins, cephalosporins, macrolides, and fluoroquinolones. If MRSA, trimethoprim-sulfamethoxazole, clindamycin, or tetracyclines Address the underlying predisposing conditions
Erythrasma	<ol style="list-style-type: none"> Systemic antibiotics: erythromycin and tetracycline Topical: antibiotics (clindamycin, erythromycin), antibacterial soaps, and antifungals (clotrimazole, miconazole)
Carbuncle/furuncle/abscess	<ol style="list-style-type: none"> Moist heat/warm compresses Incision and drainage Systemic antibiotics: penicillinase-resistant penicillins, clindamycin, and macrolides. If MRSA, trimethoprim-sulfamethoxazole, clindamycin, and tetracyclines Rigorous skin hygiene, mupirocin in nares for decolonization, and bleach baths

III. WORKUP Most cases of impetigo need not be routinely cultured; recalcitrant or unusual cases deserve a Gram stain and culture of the exudate.

IV. TREATMENT

- Topical Antibiotics.** First-line treatment is with topical antibiotics, either mupirocin, fusidic acid, or retapamulin ointment. Mupirocin has a low rate of contact sensitization.
- Systemic Antibiotics.** If impetigo is extensive, resistant to topical treatment or for patients with comorbidities such as atopic dermatitis or immunosuppression, systemic treatment with antibiotics may be warranted. Oral penicillinase-resistant penicillins, first-generation cephalosporins (e.g., cephalexin), amoxicillin with β -lactamase inhibitor, and macrolides (e.g., azithromycin and clarithromycin) are all effective



Figure 5-1. Impetigo. Dried stuck-on appearing “honey-crusted” lesions in a typical location. (From Goodheart HP. *Goodheart’s Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

treatments. Treatment with systemic antibiotics does not decrease the incidence of glomerulonephritis.

C. Wound Care. The lesions should be soaked three to four times a day in warm tap water or saline solution to remove the crusts, and then dressed with antibiotic ointment.

D. Monitor Untreated, Nonbullous Impetigo. This usually resolves spontaneously without scarring in 10 to 14 days.

FOLLICULITIS

I. BACKGROUND Folliculitis is usually a bacterial infection of the hair follicles. Staphylococcal infection is most common. Superficial folliculitis usually does not represent a serious problem, but deep and/or recurrent lesions of the scalp, nose, and eyelid cilia (sties) are far more distressing.

There are two uncommon but distinctive forms of folliculitis in which the pathogenic organism is a gram-negative bacterium:

1. Gram-negative folliculitis occurs in the setting of long-term antibiotic treatment of acne vulgaris. Antibiotic therapy is felt to alter the ecology of the anterior nares, allowing colonization by gram-negative organisms. In a small percentage of patients, predominantly males, dissemination to the skin will occur with the development of facial lesions.
2. *Pseudomonas* folliculitis has been associated with the use of hot tubs, swimming pools, and whirlpools. Given its ability to withstand relatively high temperatures and chlorine levels, *Pseudomonas aeruginosa* is well adapted to survive in such facilities. Hydration of the skin, sweating, occlusion, and abrasions further predispose to cutaneous infection. Although less common, viral and fungal infections can also cause folliculitis.

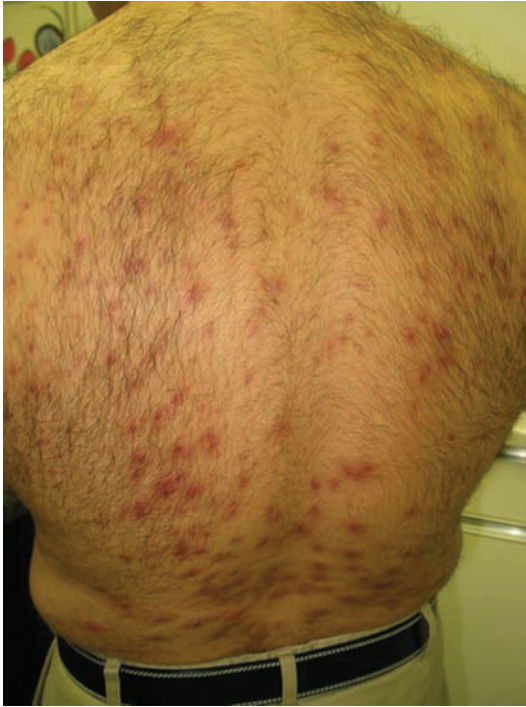


Figure 5-2. Folliculitis. Image provided by Stedman's.

II. CLINICAL PRESENTATION Folliculitis appears as superficial or deep pustules surrounding follicular units (Fig. 5-2). The superficial lesions have a central hair piercing the pustule and sometimes a red rim around the pustule. Superficial folliculitis is usually asymptomatic. The face is a common site for deep folliculitis.

Gram-negative folliculitis most often presents as superficial pustules, without comedones, on the cheeks and chin. Occasionally, there are deeper nodules and cysts. *Pseudomonas* folliculitis is polymorphous; papular, vesicular, and pustular lesions have been described. The eruption usually develops within a few days of exposure and has a predilection for the lateral trunk, axillae, buttocks, and proximal extremities. The palms and soles are spared. Patients with *Pseudomonas* folliculitis often have pruritus.

III. WORKUP Most cases of folliculitis need not be routinely cultured; recalcitrant or unusual cases deserve a Gram stain and culture of the exudate. In suspected cases of gram-negative folliculitis, culture of the nares and skin lesions is recommended. Cultures and even skin biopsies frequently fail to demonstrate any organisms in *Pseudomonas* folliculitis. A high index of suspicion, careful history taking, and, occasionally, epidemiologic investigation is necessary to establish the diagnosis.

IV. TREATMENT

- A. Topical Antibiotics.** Superficial folliculitis should respond to aggressive local hygiene and topical antibiotics such as clindamycin and mupirocin. Antibacterial soaps such as chlorhexidine (Hibiclens), Dial, or Lever 2000 are helpful as well. Recurrent disease is often secondary to colonization of *S. aureus* in the nares or groin. Mupirocin applied to anterior nares twice daily for 5 days each month can help with decolonization.
- B. Systemic Antibiotics.** Folliculitis on the male beard area is unusually recalcitrant and should be treated with oral antibiotics. Oral penicillinase-resistant penicillins, first-generation cephalosporins (e.g., cephalexin), amoxicillin with β -lactamase inhibitor, and macrolides (e.g., azithromycin and clarithromycin) can be used. *Pseudomonas* folliculitis is self-limited and typically lasts 7 to 10 days. Although it may recur, ultimately, spontaneous resolution is the rule. Ciprofloxacin can be used for severe and persistent disease. In gram-negative folliculitis, antibiotics targeted at the organism cultured from lesions may be used, although recurrences off therapy are common.
- C. Isotretinoin.** Gram-negative folliculitis may be treated with isotretinoin in recalcitrant cases.

CELLULITIS

- I. BACKGROUND** Cellulitis is a common deep dermal and subcutaneous infection. The most common etiologic organisms are *Streptococcus pyogenes* and *S. aureus*. Risk factors for developing cellulitis include venous insufficiency, lymphedema, skin trauma, chronic ulcers, chronic tinea pedis with web space maceration, diabetes, alcoholism, IV drug use, and immunosuppression.
- II. CLINICAL PRESENTATION** Cellulitis is characterized by poorly demarcated erythema, warmth, edema, and tenderness (Fig. 5-3). Lymphangitis and adenopathy may be present. Systemic symptoms such as fevers, chills, and malaise may accompany the cutaneous eruption.
- III. WORKUP** Cellulitis is a clinical diagnosis. The white cell count may be normal or slightly elevated, and blood cultures are usually negative. Skin biopsies are not recommended.

IV. TREATMENT

- 1. Systemic Antibiotics.** Oral antibiotics are the treatment of choice for cellulitis. Penicillinase-resistant penicillins, first-generation cephalosporins, amoxicillin with β -lactamase inhibitor, clindamycin, or macrolides can be used. If community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected, either trimethoprim-sulfamethoxazole, clindamycin, or tetracyclines should be used. For disease resistant to oral treatment or in septic patients, intravenous antibiotics such as vancomycin, linezolid, and daptomycin are indicated. Cellulitis associated with diabetic ulcers requires broad-spectrum coverage.



Figure 5-3. Cellulitis. (From Berg D, Worzala K. *Atlas of Adult Physical Diagnosis*. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)

2. **Treat Predisposing Conditions.** In patients with recurrent disease, underlying predisposing conditions such as venous insufficiency, lymphedema, and chronic tinea pedis need to be addressed.

ERYTHRASMA

I. BACKGROUND Erythrasma, a mild, chronic, localized, superficial infection involving intertriginous areas of skin, is caused by *Corynebacterium minutissimum*. This organism is often part of the normal flora, and some change in the host–parasite relationship, such as increased heat and humidity, results in the development of the clinical disorder.

II. CLINICAL PRESENTATION Erythrasma may be seen as dry, smooth to slightly creased or scaly, sharply marginated, red-brown plaques in the inguinal, axillary, or inframammary folds (Fig. 5-4); as mild scaling or fissuring between the third to fourth and fourth to fifth toe webs; or as generalized scaly patches. Lesions may be easily mistaken for those of superficial fungal infection. Erythrasma is usually asymptomatic.

III. WORKUP Erythrasma is diagnosed by the characteristic coral red fluorescence of lesions when viewed under the Wood light. Fluorescence is caused by



Figure 5-4. Erythrasma. (From Berg D, Worzala K. *Atlas of Adult Physical Diagnosis*. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)

a water-soluble porphyrin and may be lacking if the patient has bathed recently. Culture is rarely required and needs special media.

IV. TREATMENT

- A. Systemic Antibiotics.** Erythrasma responds best to oral erythromycin or tetracycline.
- B. Topical Treatment.** Topical antibiotics (e.g., clindamycin and erythromycin), antibacterial soaps, or azole creams (e.g., clotrimazole and miconazole) can be used alone or in conjunction with systemic antibiotics. Topical therapy alone can be effective although recurrence rates are higher.

FURUNCLE/CARBUNCLE/ABSCCESS

- I. BACKGROUND** A furuncle involves a follicle and surrounding tissue and may develop from a superficial staphylococcal folliculitis. Furuncles are common in areas of hair-bearing skin subject to friction and maceration, especially the face, scalp, buttocks, and axillae. A group of furuncles constitutes a

carbuncle. These drain at multiple points and are commonly located on the back of the neck, back, and thighs. *S. aureus* is the most common organism.

Abscesses are walled-off collections of pus, often larger and deeper than furuncles. They may develop on hair-bearing or non-hair-bearing sites and have the same predisposing conditions as furuncles.

II. CLINICAL PRESENTATION Furuncles start as firm, red, tender nodules that become fluctuant and rupture, discharging a core of necrotic tissue. Carbuncles appear similar to furuncles but drain at multiple points (Fig. 5-5). Abscesses present as tender fluctuant nodules. Furuncles, carbuncles, and abscesses can be exquisitely painful.

III. WORKUP Culture of abscesses, furuncles, and carbuncles will help tailor antibiotic therapy.

IV. TREATMENT

- A. Heat Compress.** Moist heat facilitates drainage of the purulent material from simple furunculosis.
- B. Incision and Drainage.** Deeper furuncles, carbuncles, and abscesses should be carefully and conservatively incised and drained.
- C. Systemic Antibiotics.** Furuncles, carbuncles, or abscesses associated with a surrounding cellulitis or those associated with fever or located on the face should be treated with an oral penicillinase-resistant penicillin, erythromycin, or clindamycin, and closely monitored. Systemic antibiotics should also be considered in immunocompromised patients. Given emergence of community-acquired MRSA, cultures should be obtained when possible and antimicrobial therapy tailored to the result.



Figure 5-5. Carbuncle. (From Berg D, Worzala K. *Atlas of Adult Physical Diagnosis*. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)

D. Hygiene and Decolonization Practices. Rigorous topical hygiene is important, especially in the setting of recurrent furunculosis. Topical mupirocin application in nares as described above can be helpful in decolonization. Use of bleach baths can also help decrease recurrence. Brushless shaving cream or soap alone should be used when shaving and blades discarded daily. Separate towels, washcloths, sheets, and clothing should be used; they should be laundered in hot water and changed daily. Dressings must be changed frequently and disposed of immediately. Paper tissues should be used instead of handkerchiefs.

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Suggested Readings

- Bailey E, Kroshinsky D. Cellulitis: diagnosis and management. *Dermatol Ther*. 2011;24:229-239.
- Bernard P. Management of common bacterial infections of the skin. *Curr Opin Infect Dis*. 2008;21:122-128.
- Brown J, Shriner DL, Schwartz RA, Janniger CK. Impetigo: an update. *Int J Dermatol*. 2003;42:251-255.
- Daum RS. Clinical practice. Skin and soft-tissue infections caused by methicillin-resistant *Staphylococcus aureus*. *N Engl J Med*. 2007;357:380-390.
- Holdiness MR. Management of cutaneous erythrasma. *Drugs*. 2002;62:1131-1141.
- Koning S, van der Sande R, Verhagen AP, et al. Interventions for impetigo. *Cochrane Database Syst Rev*. 2012;1:CD003261.
- Luelmo-Aguilar J, Santandreu MS. Folliculitis: recognition and management. *Am J Clin Dermatol*. 2004;5:301-310.

SPIDERS

I. BACKGROUND Spider bites are common, but most species cause minimal or no harm to humans. Approximately 14% of deaths from venomous animals result from spider bites. The species that most commonly cause severe reactions in humans in the United States are the black widow spider (*Latrodectus mactans*) and the brown recluse spider (*Loxosceles reclusa*).

The black widow spider is found throughout the United States and commonly lives in wood piles. The species is identified by a distinct red hourglass on its abdomen. It injects venom containing the neurotoxin α -latrotoxin into its prey. α -Latrotoxin destabilizes nerve cell membranes by opening ionic channels, causing irreversible acetylcholine release.

The brown recluse spider is endemic to the Midwest United States. Geographical distribution may be expanding with climate change, although many reports of bites are likely due to spider misidentification or misdiagnosis. The brown recluse spider has long legs compared with its body. It is recognized by its yellow-brown color and violin string marking on its back. The brown recluse spider injects sphingomyelinase D which triggers platelet aggregation, endothelial hyperpermeability, hemolysis, and neutrophil-induced skin necrosis. It typically only bites when threatened.

II. CLINICAL PRESENTATION Black widow bites are sensed as a pinprick, followed by a dull aching pain. After about 30 minutes, the skin surrounding the bite may feel numb. The skin appears erythematous and mildly edematous with local piloerection. In addition, there may be local perspiration and lymphangitis. Peaking between 1 and 8 hours after the bite, a systemic anticholinergic response may last up to 2 days (Table 6-1). A characteristic facial swelling, known as *Latrodectus* facies, can also be seen. Death occurs in less than 1% of all black widow bites.

Brown recluse bites cause local reactions that range from a mild local burning sensation to severe cutaneous necrosis. Severe reactions are seen in less than 10% of bites. Severe reactions generally begin as localized edema with an erythematous halo, resembling a “bull’s-eye.” Over the next 12 hours, bullae form centrally. The plaque forms an irregularly shaped blue-black eschar, surrounded by pallor and a larger area of erythema, forming the characteristic “red, white, and blue sign.” Less serious lesions heal over weeks while more severe bites heal over months and may leave a residual scar. Associated systemic symptoms are listed in Table 6-1. Death may result from acute renal failure or intravascular hemolysis, usually 2 to 3 days following the bite.

TABLE 6-1 Systemic Symptoms to Spider Bites

<i>Black Widow Spider</i> (toxin = α -latrotoxin)
Miosis
Lacrimation
Sialorrhea
Hyperhidrosis
Bronchospasm
Bradycardia
Abdominal cramping and diarrhea
Increased urination
Skeletal muscle spasm and rigidity
<i>Brown Recluse Spider</i> (toxin = sphingomyelinase D)
Fever
Morbilliform rash
Arthralgias
Nausea and vomiting
Respiratory failure (pulmonary edema)
Anemia due to intravascular hemolysis
Disseminated intravascular coagulation
Renal failure
Rhabdomyolysis

III. WORKUP Diagnosis of a spider bite can be difficult clinically due to a broad differential diagnosis (Table 6-2). Ideally the offending spider is captured for identification. Wounds can be cultured to evaluate for superinfection. Skin biopsy may reveal neutrophilic perivascularitis, hemorrhage, edema, necrosis, and a prominent eosinophilic and neutrophilic infiltrate which may involve the subcutaneous fat. Workup for systemic involvement should include a sedimentation rate, complete blood count, fibrinogen, coagulation studies, urinalysis, and renal function studies.

IV. TREATMENT Treatment of mild black widow spider bites includes ice and/or topical corticosteroid. For more severe reactions, a tourniquet should be applied to occlude venous return. Pain medication and muscle relaxants should be utilized as needed. Benzodiazepines and intravenous calcium gluconate help relieve tetany. Antivenin may reduce complications not relieved by other agents. Severe reactions should be managed in a facility prepared to handle cardiovascular and respiratory emergencies (Table 6-3).

TABLE 6-2**Differential Diagnosis for Spider Bites**

Allergic contact dermatitis
 Deep fungal infection
 Diabetic ulceration
 Lyme disease
 Other bite
 Pyoderma gangrenosum
 Staphylococcal infection
 Venous stasis ulceration

TABLE 6-3**Primary Treatment Options for Severe Spider Bites****Black Widow Spider**

1. IV calcium gluconate
2. Benzodiazepines
3. Antivenin

Brown Recluse Spider

1. Oral prednisone
2. Antivenin
3. Dapsone
4. Colchicine
5. Hyperbaric oxygen

Mild brown recluse spider bites typically heal well with local wound care, including ice, elevation, and avoidance of strenuous exercise. Antibiotics (erythromycin or cephalosporins) and aspirin may yield a more favorable outcome. If lesions progress or there are signs of systemic involvement, dapsone (after checking glucose-6-phosphate dehydrogenase levels), colchicine, and prednisone have yielded inconsistent outcomes. Antivenin can be considered if available. Hyperbaric oxygen may speed healing of the skin (Table 6-3).

SNAKES

I. BACKGROUND Between 4,000 and 6,000 venomous snakebites occur annually in the United States. The two families of snakes of medical importance in the United States include the Viperidae and Elapidae families.

The Viperidae family, or pit viper snakes, include rattlesnakes, cottonmouth (water moccasin), and copperhead varieties. They are recognized by their triangular head, elliptical “cat’s eye” pupils, single row of ventral scales,

and depressed heat-sensing facial pit. Eighty percent of bites result in injection of venom. Pit viper venom has hemorrhagic and coagulopathic properties and may contain presynaptic neurotoxins. Bites from the diamondback rattlesnake account for 95% of Viperidae fatalities.

The Elapidae family includes the coral snake whose venom causes fibrinolysis, anaphylaxis (via activation of the complement cascade), and neurotoxicity. They are recognized by their round eyes, and red, yellow, or white bands. In the United States, they mimic the nonvenomous King snake which has red and black bands. The distinction can be remembered by “Red on yellow, kill a fellow; red on black, venom lacks.”

II. CLINICAL PRESENTATION Pit viper bites result in immediate local pain and visible fang puncta. Initial weakness, swelling, paresthesias, nausea, and vomiting ensue. Local reactions due to direct tissue injury and victim cytokine responses include ecchymoses, tenderness, bullae formation in flexure creases, and myonecrosis. Local reactions spread via lymphatics. Less common complications may include compartment syndrome and wound infection. Venom may rarely induce urticaria, angioedema, and anaphylactic reactions. Hematologic venom effects include fibrinogen degradation and destruction, manifesting as bleeding at the bite site, gingiva, or nasal mucosa. More severe presentations include gastrointestinal or intracranial hemorrhage. Systemic venom effects may cause direct cardiovascular toxicity, respiratory arrest, disseminated intravascular coagulation, acute renal failure, neurotoxicity, and rhabdomyolysis.

Coral snake bites are typically painless without local edema or necrosis. The neurotoxic effects cause limb weakness or numbness in the bitten extremity. Within hours, systemic symptoms including tremors, muscle fasciculations, sialorrhea, and bulbar paralysis (causing dysphagia, dyspnea, or total flaccid paralysis) ensue. Paralysis of the diaphragm leads to respiratory paralysis and death.

III. WORKUP Snake envenomation victims should be assessed and observed with serial examinations in facilities prepared to handle acute hematologic, neurologic, respiratory, and cardiovascular emergencies. Lab work should include type and cross, complete blood count, prothrombin time, partial thromboplastin time, fibrinogen levels, and fibrin split products.

IV. TREATMENT Envenomated extremities should be immediately immobilized and elevated in a relatively extended position ($\leq 45^\circ$ of flexion) to avoid lymphatic outflow obstruction, reduce swelling, and decrease the risk of bullae formation at flexural creases.

Antivenom for specific snake species is commercially available. Emergent treatment with antivenom is indicated in patients with progressive local tissue effects, hematologic venom effects, and other venom-related systemic signs. Pit viper limb envenomation presenting with nonprogressive localized pain and swelling as the only clinical manifestation does not require antivenom. However, some experts still treat with antivenom if the swelling crosses a major joint or involves the hand in an attempt to improve limb functional outcomes. Continued monitoring is important following stabilization due to the potential

for recurrent envenomation reactions that may occur despite initial control with antivenom. In addition, patients given antivenom should be monitored for anaphylactoid reactions.

Opioids are preferred over nonsteroidal anti-inflammatory agents (NSAIDs) due to the theoretical risk of increased bleeding with NSAIDs in a potentially coagulopathic or thrombocytopenic patient. Platelet and clotting factors should be restored by blood component transfusions as indicated. Standard age-appropriate tetanus booster recommendations should be followed as *Clostridium tetani* infection has been reported following viper envenomation. A panel of snakebite experts currently recommends against several therapies commonly used to treat pit viper envenomations (Table 6-4). Finally, notification of a certified poison center is recommended for every snake envenomation case by calling 1-800-222-1222 in the United States.

INSECTS

I. BACKGROUND The most serious reactions to insects are caused by acquired hypersensitivity. Over 80% of deaths from insect bites and stings result from anaphylactic reactions and occur within 1 hour of the event. Anaphylaxis occurs in 3% of adults and 1% of children after an insect sting. Many patients who develop generalized reactions to insect bites or stings have no history of previous systemic of local reactions to the insect. Patients with a large local reaction incur only a 5% to 10% chance of developing a systemic reaction.

TABLE 6-4 **Treatments to Avoid Following Pit Viper Snakebites**

Treatment to Avoid	Reasons for Avoidance
Wound incision and suction	Does not remove significant amounts of venom Worsens local tissue injury
Ice and cryotherapy	Associated with severe iatrogenic tissue injury
Tourniquet and pressure immobilization	May improve or worsen outcomes
Electrical current	Ineffective Causes significant tissue injury
Prophylactic fasciotomy	Antivenom alone may reduce compartment pressures
Nonsteroidal anti-inflammatory drugs	Theoretical harm from platelet dysfunction in a thrombocytopenic patient
Prophylactic antibiotics	Leads to unnecessarily prolonged hospital stays
Corticosteroids	No evidence of improved outcomes

The most venomous insects belong to the order Hymenoptera, which includes bees, wasps, and ants. Hymenoptera venom contains serotonin, kinins, acetylcholine, lecithinase, hyaluronidase, phospholipase, and melittin. Exposure to venom in allergic individuals causes histamine release from leukocytes.

The order Diptera includes mosquitoes and flies. Mosquitoes inject salivary fluid into the victim, causing an immediate allergic reaction. Flies pierce through the skin, directly inserting saliva that causes both allergic and toxic reactions.

The order Hemiptera includes the bed bug (*Cimex lenticularis*) and the Reduviid bug. Historically, bed bugs were found in poor living conditions and unkempt hotels. In recent years, infestations have increased at a rapid rate and now include suburban and higher income populations as well. Bed bugs hidden in mattresses and upholstery come out at night to feed. The Reduviid bug of Mexico, Central America, and South America lives in cracks of mud hut walls and spreads disease-depositing stool on the skin as it bites.

The Meloidae and Staphylinidae families of the order Coleoptera include blister beetles. Blister beetle species of varying colors and patterns are found worldwide, with approximately 300 species residing in the United States. When blister beetles are pressed or rubbed, pederin- or cantharidin-containing hemolymph blisters the skin. Cantharidin is a toxin of medical interest, and it is used for treatment of warts and molluscum in dermatology.

II. CLINICAL PRESENTATION

A. Hymenoptera. Hymenoptera stings usually result in instantaneous pain followed by a localized wheal and flare reaction with associated pruritus. Edema is variable (Fig. 6-1). Multiple bee, wasp, yellow jacket, or hornet



Figure 6-1. Angioedema due to a bee sting. This patient developed an immediate hypersensitivity reaction after being bitten on the lip. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

stings can result in systemic reactions, including vomiting, diarrhea, generalized edema, dyspnea, hypotension, and collapse. Life-threatening allergic sting reactions are characterized by the usual manifestations of anaphylaxis: urticaria, laryngeal edema, bronchospasm, abdominal cramps, and shock. Harvester and fire ants are known for the intense burning and pain associated with their stings. Localized necrosis secondary to phospholipase and hyaluronidase in the venom may be present at the sting site.

B. Diptera

1. **Mosquitoes.** Mosquito bites result in immediate allergic reaction to injected salivary fluids. Several hours later, a pruritic papule develops. Mosquitoes can also serve as the host for diseases, including Eastern and Western Equine Encephalitis, West Nile Virus, filariasis, malaria, and yellow fever.
2. **Flies.** Flies bites cause immediate pruritic wheals followed by itchy, red papules. The black fly is renowned for inducing extremely painful and long-lasting reactions. Flies associated with disease are listed in Table 6-5.

C. Siphonaptera (Fleas). Bites usually appear as grouped urticaria papules, often with a central punctum. They are commonly located on the distal extremities. Fleas are vectors for the bubonic plague, brucellosis, melioidosis, erysipeloid, and endemic typhus.

D. Hemiptera (True Bugs). Bed bugs leave linearly arranged pruritic papules in groups of two or three on the face and extremities, known as the “breakfast, lunch, and dinner” sign. The Reduviid bug acts as a vector for *Trypanosoma cruzi*, causing American trypanosomiasis or Chagas disease. Known as the “kissing bug,” the Reduviid often bites the victim’s face. Local reactions include a unilateral periorbital conjunctivitis and periorbital edema, known as the “Roma-a sign,” and regional lymphadenopathy

TABLE 6-5 Fly-Associated Disease

Fly	Geography	Disease	Clinical Features
Botfly (<i>Dermatobia hominis</i>)	Mexico Central America South America	Myiasis	Painful furuncles due to deposition of parasitic larvae
Black fly (<i>Simulium</i>)	Mexico South America	Onchocerciasis	Facial edema Pruritic dermatitis Subcutaneous nodules Lymphatic obstruction Iritis
Sandfly (<i>Phlebotomus</i> and <i>Lutzomyia</i>)	Middle East Africa Asia Central America South America	Leishmaniasis	Scarring circular ulcerations Mucocutaneous lesions Visceral disease

known as the “Chagoma.” Systemic reactions include myocardial damage, megacolon, and megaesophagus.

- E. Coleoptera (Beetles).** Localized painful vesicles and bullae appear immediately following cutaneous contact with pederin or cantharidin from the blister beetle. Lesions can be in a linear distribution or kissing distribution (if the beetle is crushed in skin folds).

III. WORKUP Diagnosis of insect bites typically relies on history and physical examination. A thorough investigation of possible exposures including travel history and living conditions is helpful. If the suspected insect is a known vector for disease, the patient should be monitored closely for possible systemic findings.

Patients with systemic reactions to stinging insects should undergo testing for specific immunoglobulin E (IgE) antibodies to stinging insects. For patients with negative skin test responses but a convincing history of stinging insect hypersensitivity, an in vitro IgE antibody test or repeat skin testing may be considered for further workup. A history of recurrent and severe anaphylaxis may prompt a workup for mast cell disorders, including serum tryptase level and bone marrow biopsy.

IV. TREATMENT Insects noted on the skin should be flicked or brushed away. Insects or their stingers should not be squeezed as this action may further release venom (avoid using forceps). Cold packs, systemic antihistamines, and topical steroids may relieve pruritus and inflammation from local reactions.

Adult patients with acute anaphylaxis following insect sting should be given 0.3 to 0.5 mL of epinephrine 1:1,000 IM immediately and then every 5 to 15 minutes as needed. Children are given a dose of 0.01 mL/kg (maximum dose of 0.3 mL). Lower doses should be used in the elderly or patients with cardiovascular issues. Intravenous epinephrine in a 1:10,000 dilution in 0.1 mg boluses can be administered in the setting of profound hypotension and poor peripheral circulation until symptoms improve. Hypotensive patients should be given intravenous fluids and placed in a recumbent position. Parenteral or oral diphenhydramine and ranitidine can be given in combination to stabilized patients. In more severe reactions, steroids may help prevent biphasic anaphylactic responses. Inhaled β_2 -agonists such as salbutamol are useful in patients with bronchospasm. Following the initial reaction, patients should be advised that a second wave of reactivity may occur within hours to 2 days following the initial episode, and patients should be monitored accordingly.

Patients with a history of systemic reactions to an insect sting should be educated on insect avoidance behaviors. These behaviors include wearing protective clothing and avoidance of insect attractants (perfumes or brightly colored clothing). Medical identification indicating stinging insect hypersensitivity may be worn. These patients should always carry epinephrine and be educated on the appropriate indications and methods for administration. There is no contraindication to the use of epinephrine in a life-threatening situation such as anaphylaxis, even in patients with known hypertension or cardiac arrhythmias. Immunotherapy to insect venom or fire ant whole-body extract should be considered in patients with positive skin testing for stinging insect hypersensitivity.

Insect repellents containing diethyltoluamide (DEET) offer the most effective protection against mosquitoes, flies, fleas, mites, and ticks. Ethyl hexanediol, dimethyl phthalate, and dimethyl carbate butopyronoxyl provide a narrower spectrum of prevention compared with DEET. Use of a combination of these repellants improves effectiveness. Repellants form a barrier against penetration that extends <4 cm away from the skin. DEET also blocks the mosquitoes ability to track human carbon dioxide vapor trails. Repellants do not mask other insect stimuli such as sweat, moisture, and warmth. DEET protection lasts about 10 to 12 hours at room temperature, but can be shortened by clothing friction, water, sweat, wind, or heat. Repellants may last several days on fabrics. Mosquito nets and clothing should also be used in areas where mosquitoes serve as vectors for disease.

MITES

I. BACKGROUND Mites are a form of arachnid that parasitize humans and feed on organic matter. Depending on the type of mite, a range of dermatologic manifestations are seen.

II. CLINICAL PRESENTATION Mite infestations manifest as papulo-squamous, urticarial, inflammatory, or even bullous dermatoses. They are also responsible for transmitting infectious diseases. Clinical manifestations and diseases associated with specific mites are outlined in Table 6-6. *Cheyletiella* mites eat keratin on small mammals, giving dogs and cats “walking dandruff.”

TABLE 6-6	Mite-Associated Disease	
Mite	Associated Disease	Treatment
<i>Acarus</i> (grain mite)	Baker itch	Pest control Symptomatic relief ^a
<i>Allodermanyssus sanguineus</i> (house mouse mite)	Rickettsial pox	Doxycycline ^b
<i>Cheyletiella</i>	Walking dandruff	Treat pets: - Ectoparasitic shampoos and dips) - Permethrin spray - Fipronil spray - Topical amitraz Symptomatic relief ^a
<i>Demodex</i>	Rosacea	Topical sulfur (initial treatment) Other topicals: - Permethrin 5% - Salicylic acid

(Continued)

TABLE 6-6 Mite-Associated Disease (Continued)

		<ul style="list-style-type: none">- Metronidazole- Crothamiton- Lindane- Retinoids Oral ivermectin Oral retinoids
<i>Dermanyssus</i> (fowl mite)	Equine encephalitis	Removal of infested birds and nests
<i>Ornithonyssus</i> (fowl mite)	Western equine encephalitis	House cleaning and fumigation Symptomatic relief ^a Topical acaricides <ul style="list-style-type: none">- Gamma benzene hexachloride 1%- Crothamiton- Permethrin- Malathion
<i>Dermatophagoides</i> (dust mite)	Allergic reactions Atopic dermatitis	Humidity < 50% Mattress and pillow protective coverings Wash bedding once weekly in hot water Symptomatic relief ^a
<i>Glycyphagus</i> (cheese mite)	Grocer itch	Pest control Symptomatic relief ^a
<i>Sarcoptes scabiei</i> (scabies mite)	Pruritic dermatitis	Wash clothes and bedding in hot water Pest control Topical permethrin Oral ivermectin
<i>Trombicula</i> (chigger mite)	Dermatitis and scrub typhus	Symptomatic relief, ^a additionally: <ul style="list-style-type: none">- Antipruritics: camphor, menthol- Topical anesthetics with pramoxine- Potent topical corticosteroids under occlusion- Ice application- Excision of refractory lesions

^aSymptomatic relief for mite-associated dermatitis includes topical corticosteroids and oral antihistamines. ^bAntibiotics may shorten the duration of symptoms. Second-line antibiotics include erythromycin, tetracycline, and chloramphenicol.

Humans who handle affected mammals may develop pruritic dermatitis. The scabies mite burrows under the epidermis, leaving behind eggs and feces. Pruritic papules are commonly found in interdigital spaces, palms, flexor wrists, umbilicus, axilla, and genitalia. Chiggers hatch larvae on the ground that penetrate the stratum corneum on the feet and ankles of mammalian hosts, leaving behind grouped pruritic papules, papulovesicles, or urticarial wheals (Fig. 6-2). Lesions are also seen in areas where clothing restricts the movement of the mites. Hypersensitivity to chiggers can lead to “summer penile syndrome” in which there is seasonal penile swelling. They also transmit scrub typhus which presents with a black eschar at the inoculation site and progresses to pneumonitis and constitutional symptoms. *Demodex* mites are asymptomatic, but are often found in hair follicles and sebaceous glands. They may be associated with rosacea and folliculitis. Grain and cheese mites cause contact dermatitis reactions in agricultural workers. The foul mite, *Dermanyssus americanus*, rarely manifests as bites, and more commonly causes a diffuse eczematous dermatitis in the late spring.

III. WORKUP Diagnostic use of adhesive tape, dermoscopy, and skin scraping can be used to aid in visualization of burrows, eggs, feces, larvae, or mites (Fig. 6-3). Skin biopsy may also be useful.



Figure 6-2. Chigger bites. This person was bitten while walking barefoot in tall grass. These lesions are intensely pruritic. Chiggers are nonscabetic harvest mites. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

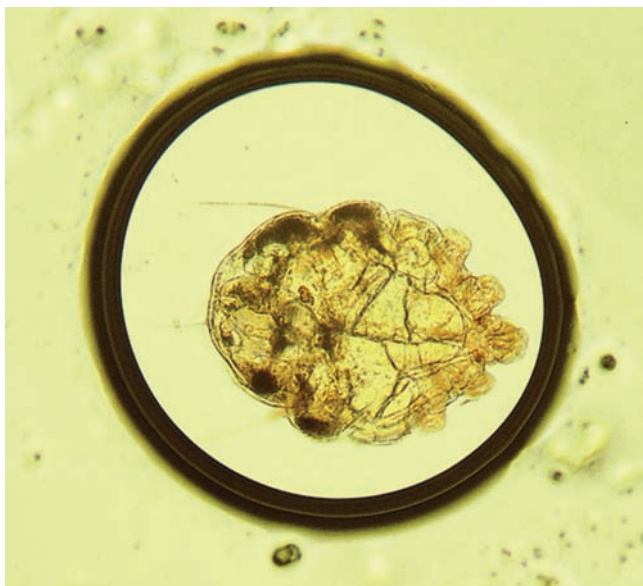


Figure 6-3. Microscopy of a skin scraping often demonstrates the presence of mites in patients with scabies. (From Fleisher GR, Ludwig S, Baskin MN. *Atlas of Pediatric Emergency Medicine*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

IV. TREATMENT Methods to prevent infestation include pretreatment of clothing with permethrin and DEET. Infected pets should be treated. Bedding should be cleansed thoroughly to prevent reinfection. Treatment depends on the type of mite and is outlined in Table 6-6.

CATERPILLARS AND MOTHS

I. BACKGROUND Caterpillars and moths are from the order Lepidoptera, which includes 165,000 species worldwide and 11,000 species in the United States. Twelve percent of these species cause harm to humans. Some caterpillars bear specialized nettles or hairs that irritate their predators, while others possess spines or setae that break away during attacks. Caterpillars that possess venom in their hairs or spines are classified as phanerototoxic. Caterpillars that circulate venom only in their hemolymph are classified as cryptotoxic. Caterpillar venom contains proteolytic enzymes, kinins, plasminogen activators, and histamine. Reports of caterpillar-induced reactions have increased since the 1970s.

II. CLINICAL PRESENTATION Caterpillar-associated illness can be categorized into the following systemic classifications:

- **Erucism:** Skin findings characterized by localized and pruritic macular, papular, or vesicular contact dermatitis or urticaria caused by direct contact

or airborne exposure to hairs, spines, or hemolymph from larval forms. *Megalopyge opercularis* is known for causing a characteristic grid-like painful petechial eruption caused by direct contact with its parallel rows of dorsal spines. The reaction can progress to cause lymphadenopathy, pseudoparalysis, muscle spasm, and even shock-like symptoms.

- **Lepidopterism:** Systemic illness characterized by generalized urticaria, headache, conjunctivitis, pharyngitis, bronchospasm, nausea, and vomiting caused by direct or airborne exposure to hairs, spines, or hemolymph.
- **Dendrolimiasis:** Chronic urticaria, migratory inflammatory polyarthritis and polychondritis, osteoarthritis, and acute scleritis caused by direct contact with hairs, spines, or hemolymph of living or dead *Dendrolimus pini* caterpillars or cocoons. An IgE-mediated acute hypersensitivity is followed by a chronic autoimmune-mediated bone and joint disease.
- **Pararamose:** Pruritic and painful dermatitis that is associated with arthritis and ankylosing joint deformity following contact with *Premolis semirufa*.
- **Ophthalmia Nodosa:** Initial conjunctivitis is followed by chronic panuveitis caused by intraocular migration of hairs from lymantriid caterpillars and moths. Note that this syndrome is more commonly seen in tarantula owners.
- **Consumptive Coagulopathy with Secondary Fibrinolysis (Lonomism):** Following the immediate bleeding and ecchymosis at the sting site, spontaneous bleeding ensues from the mucous membranes, gastrointestinal tract, and urogenital tract. Victims may die rapidly of intracerebral hemorrhage or acute renal failure if not treated promptly.
- **Seasonal Ataxia:** Patients develop unsteady gait and dysarthria following ingestion of the caterpillar *Anaphe venata*, which contain high levels of thiaminase causing thiamine deficiency when consumed. This caterpillar is a primary protein source for many populations in Nigeria during the rainy season.

Species that commonly cause the above syndromes are outlined in Table 6-7.

III. WORKUP Diagnosis of caterpillar envenomation typically relies on a thorough history as clinical findings can be nonspecific. Unilateral eye involvement should prompt a slit-lamp examination to look for setae. Cutaneous bruising in South America should prompt laboratory evaluation for coagulopathy that may suggest lonomism. Pathology is not diagnostic and usually shows epidermal edema, a perivascular lymphocytic infiltrate, and eosinophils similar to an arthropod reaction; some species may leave behind embedded spines.

IV. TREATMENT Prevention is the key to management. Patients should be educated to avoid handling caterpillar species intentionally. Highly sensitive individuals should avoid infested areas and wear protective clothing. Manual removal of egg nests, caterpillars, and cocoons should be performed during infestations. Pesticides, including *Bacillus thuringiensis* and diflubenzuron, have also been used for infestations.

If there is contact with a caterpillar, spines should not be brushed off as they may break off and remain embedded in the skin. Large larvae can be removed with forceps or stripped off with cellophane tape. The affected area should be cleansed with soap and water. Clothing should be laundered. Constrictive clothing or jewelry should be removed in case of impending limb swelling.

Specific treatments for caterpillar syndromes are listed in Table 6-8.

TABLE 6-7 Syndromic Classification and Treatments of Common Caterpillar Envenomation				
Syndrome Classification	Species	Common Name	Species Identification	Geographical Distribution
Erucism	<i>Automeris io</i>	Io moth	Red and white lateral stripes	North America
	<i>Sibine stimulea</i>	Saddleback	Brown or purple saddle on a green blanket	North America
	<i>Megalopyge opercularis</i>	Puss	Cotton ball	North America
Lepidopterism	<i>Lymantria dispar</i>	Gypsy	Five pairs of blue spots and six pairs of red spots	Eastern United States Australia Europe
	<i>Euproctis</i> spp.	Browntail	Dorsal red spots, white hairs on the sides	Eastern United States Europe Northern Africa Canary Islands
	<i>Thaumetopoea</i> spp. <i>Ochrogaster</i> spp.	Processionary tree	Caterpillars line up in a long row like a freight train	Australia Europe China Japan
Dendrolimiasis	<i>Dendrolimus pini</i>	Pine-tree lappet moth	Dorsal brown diamonds outlined by black and white	Europe China
Pararamose	<i>Premolis semirufa</i>	Pararama	Brown, found in bowls of sap-collectors in the Amazon	South America
Ophthalmia nodosa	Various	Various	Hairs	Worldwide
Coagulopathy and fibrinolysis (lonomism)	<i>Lonomia obliqua</i> and <i>L. achelous</i>	Saturniid moth	Well camouflaged green to light brown	South America
Seasonal ataxia	<i>Anaphe venata</i>	African silkworm	Found in rainforest	Africa

TABLE 6-8 **Treatments for Caterpillar Syndromes**

Syndrome	Treatment
Erucism and lepidopterism	<p>Pruritus:</p> <ul style="list-style-type: none"> • Topical antipruritics: camphor, menthol 0.5%, pramoxine 1% several times daily as needed • Topical corticosteroids once to twice daily as needed • Oral antihistamines <p>Pseudolymphomatous nodules:</p> <ul style="list-style-type: none"> • Intralesional corticosteroids (triamcinolone 5–10 mg/mL) <p>Severe cases:</p> <ul style="list-style-type: none"> • Oral prednisone 1 mg/kg/d with 2- to 3-wk taper • Intramuscular triamcinolone 40 mg <p>Pain:</p> <ul style="list-style-type: none"> • Ice application • Oral analgesics <p>Muscle spasm (<i>Megalopyge</i>):</p> <ul style="list-style-type: none"> • Intravenous diazepam 5 mg • Intravenous 10% calcium gluconate 10 mL
Dendrolimiasis	<p>Pruritus: oral antihistamines</p> <p>Joint disease:</p> <ul style="list-style-type: none"> • Oral analgesics • Surgical correction • Drainage of purulent joint space
Lononism	<p>Consult hematology</p> <p>Distinguish between <i>Lonomia obliqua</i> and <i>L. achelous</i> species</p> <ul style="list-style-type: none"> • Treat <i>L. achelous</i> with cryoprecipitate, purified fibrinogen, antifibrinolytics • Do NOT treat <i>L. obliqua</i> (may exacerbate condition) • Do NOT give fresh frozen plasma or whole blood for either species (may exacerbate condition) • Intravenous <i>L. obliqua</i> antivenom 10.5 mg within 24–48 h
Ophthalmia nodosa	<p>Pain:</p> <ul style="list-style-type: none"> • Copious irrigation • Removal of hairs <p>Uveitis or iritis</p> <ul style="list-style-type: none"> • Topical corticosteroids <p>Granulomas</p> <ul style="list-style-type: none"> • Surgical removal <p>Severe intraocular reactions</p> <ul style="list-style-type: none"> • Oral steroids <p>Refractory cases</p> <ul style="list-style-type: none"> • Vitrectomy • Enucleation
Seasonal ataxia	Oral thiamine hydrochloride 100 mg every 8 h

MARINE STINGS

I. BACKGROUND Most venomous sea life is found in the warm waters of the tropics and subtropics. The phylum Cnidarian includes venomous jellyfish, box jellies, sea anemones, and corals. Cnidaria contain stinging capsules called nematocysts which contain toxins. Jellyfish are found throughout the world, and their stings are the most common marine injury. In Seabather's eruption, cnidarian larvae (most commonly of the Thimble jellyfish *Linuche unguiculata* and sea anemone *Edwardsiella lineate* species) become entrapped under bathing attire and discharge toxins from their nematocysts. Outbreaks have occurred in the Caribbean, Bermuda, and United States eastern seaboard.

Stingrays have serrated barbs on their tails, which contain venom that is both cardiotoxic and neurotoxic. Vasoconstrictive properties of the venom also cause tissue necrosis and poor wound healing. Stingrays reflexively lash their tail when provoked or stepped on while buried in the sand. The barb may detach and remain in the wound. There are about 1,500 stingray injuries annually in the United States.

II. CLINICAL PRESENTATION Initial contact with nematocyst toxins causes a sharp burning sensation. In mild stings, erythematous welts appear. Stings appear in a flagellate or whip-like pattern (Fig. 6-4). Welts may subside



Figure 6-4. Jellyfish sting. Note the curvilinear, whiplike shape of the lesions. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

within hours leaving behind postinflammatory hyperpigmentation. Acute responses may be accompanied by urticaria, angioedema, or anaphylaxis. A small percentage of patients also have a secondary delayed-type hypersensitivity reaction a few weeks later in which new pruritic lichenoid papules and plaques appear in sites of previous involvement. More severe stings may progress to bullae or even tissue necrosis. Systemic symptoms may include abdominal distress, chest tightness, and dyspnea. Death may occur only a few minutes after contact with the Box jellyfish (*Chironex fleckeri*).

Seabather's eruption also begins with a sharp burning sensation. Self-limited edematous wheals appear under the bathing garments.

Stingray envenomation presents with pain and swelling at the site. Wounds commonly become necrotic and ulcerated. Patients are at risk for infection with marine organisms including *Vibrio* and *Aeromonas* species. Rarely, arterial laceration and compartment syndrome can complicate envenomation. Other symptoms include muscle cramps, salivation, headaches, abdominal distress, dyspnea, seizures, and cardiac arrhythmias. Death typically occurs from immediate exsanguination or penetration of a vital organ.

III. WORKUP Diagnosis is usually apparent given a history of a sting in marine waters. Tape stripping to remove nematocysts may help confirm the diagnosis of Cnidarian stings. Biopsy may show nematocysts penetrating the epidermis and papillary dermis. Stingray wounds may require imaging to look for foreign bodies.

IV. TREATMENT Prevention of marine stings is key. If stung, the swimmer should be immediately removed from the water to avoid drowning. Vital signs should be monitored, and transfer to an acute care facility may be necessary depending on sting severity. Soaking the injury in hot water denatures most toxins. In Seabather's eruption, the bathing garment should be removed and the affected area should be rinsed off. Household vinegar (acetic acid 5%) blocks the discharge of remaining nematocysts and should be applied liberally to Cnidarian stings. Freshwater will cause massive discharge from remaining nematocysts and should be avoided. Anecdotal treatment methods of Cnidarian stings include bicarbonate, meat tenderizer (although may cause contact dermatitis), lemon or lime (although may cause phytophotodermatitis), and concentrated urine due to its ammonia content. Topical corticosteroids may be used to control prolonged symptoms. There is antivenom available for *Chironex fleckeri* envenomation.

Stingray stings should be treated with supportive care in an acute care facility if necessary. Wounds should be cleansed thoroughly and debrided if necrotic. Closure should be delayed due to high risk of infection. Tetanus prophylaxis should be administered as appropriate. Prophylactic antibiotics should be administered to immunocompromised patients or if there is a residual foreign body.

MAMMALIAN BITES

I. BACKGROUND Dog bites are the most common animal bite in the United States with an estimated 4.7 million dog bites occurring annually.

Dog bites constitute about 85% to 90% of mammalian bites followed by cats (5% to 10%), rodents (2% to 3%), and humans (2% to 3%).

Risk factors for dog bites include children under 5 years of age, male gender, household dogs, and male unsterilized dogs.

Risk of infection varies depending on the species. Dog bites are infected about 18% of the time, usually with *Pasteurella canis* (Fig. 6-5). Infection risk from cat bites varies from 28% to 80%, and the most common infection is *Pasteurella multocida*. *Bartonella henselae* can be transmitted by both cat scratches and bites. Rodent bites have an infection rate of 10%. Rat-bite fever is caused by *Streptobacillus moniliformis* or *Spirillum minus*. Most human bites cause deep puncture wounds leading to polymicrobial infections. Of note, *Eikenella corrodens* can cause septic arthritis after a human penetrating bite to the hand or infective endocarditis. Hepatitis B, hepatitis C, and human immunodeficiency virus have all been transmitted via human bites.

II. CLINICAL PRESENTATION Animal bites range from small scratches to severe bites that involve muscle, tendons, or fractured bone. Cat bites create deep punctures due to their long, pointy teeth. Human bites typically occur on the fingers. Adult human bite marks have an intercanine distance of >3 cm, and when present on children raises concern for abuse.

III. WORKUP A thorough history should be obtained including information about the attack circumstances, medical comorbidities, immunization status, and hand dominance. Examination includes wound exploration to identify



Figure 6-5. This 12-year-old girl had been bitten by her dog and later hospitalized for cellulitis that improved on intravenous antimicrobials. (From Fleisher GR, Ludwig S, Baskin MN. *Atlas of Pediatric Emergency Medicine*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

foreign bodies and tissue types involved. Motor, sensory, and vascular function should be assessed. The patient should be evaluated for signs of infection, including fever, purulent drainage, and lymphadenopathy. Cultures should be obtained from wounds that appear infected clinically. Wounds at high risk for infection are managed at an acute care facility. Factors that increase the risk of infection include:

- Puncture or crush wounds (especially from cats)
- Wounds penetrating bone, joints, tendons, vascular structures, or prosthetic joints
- Wound on the hands, feet, or genitals
- Wounds presenting more than 8 hours after the injury
- Patients with edema
- Patients who are immunocompromised

Imaging may be warranted in certain circumstances. Patients with cervical lesions require cervical immobilization until cervical spine injuries are excluded with imaging. Imaging may also reveal foreign bodies such as teeth. X-rays are obtained for all clenched fist injuries, puncture wounds near joints, and penetrating scalp wounds.

IV. TREATMENT All wounds should be cleaned, irrigated, and debrided. Foreign bodies are extracted. Wounds with high risk of infection should be left open, including all human bites. If there is uncertainty regarding infection, delayed primary closure can be performed 4 to 5 days later. Wounds on the head and neck can be sutured closed with antibiotic prophylaxis because the head and neck has a large blood supply and low risk for edema. Infected wounds are treated with antibiotics covering both aerobes and anaerobes (Table 6-9). Affected limbs should be elevated during the first 2 to 3 days, and hand wounds should be immobilized for 3 to 5 days. Tetanus immunization should be given

TABLE 6-9 Antibiotics for Infected Mammalian Bites

Animal	Common Bacterial Isolates	Preferred Antibiotic Options
Dogs and cats	<i>Pasteurella</i> spp. ^a <i>Staphylococcus aureus</i> <i>Bacteroides tectum</i> <i>Fusobacterium</i> spp. <i>Capnocytophaga</i> spp. <i>Porphyromonas</i> spp.	Penicillin-tolerant patients: <ul style="list-style-type: none"> • Oral amoxicillin–clavulanate • Intravenous ampicillin–sulbactam • Intravenous ertapenem Mildly penicillin-allergic patients: <ul style="list-style-type: none"> • Oral or intravenous cefoxitin • Intravenous carbapenem Severely penicillin-allergic patients: <ul style="list-style-type: none"> • Oral doxycycline • Oral or intravenous trimethoprim–sulfamethoxazole • Oral or intravenous fluoroquinolone + clindamycin

(Continued)

TABLE 6-9	Antibiotics for Infected Mammalian Bites (Continued)	
Rats	<i>Streptobacillus moniliformis</i> <i>Spirillum minus</i>	Intravenous penicillin G Penicillin-allergic patients: <ul style="list-style-type: none">• Intravenous streptomycin• Oral tetracycline or doxycycline
Humans	<i>Streptococcus</i> spp. <i>S. aureus</i> <i>Eikenella corrodens</i> ^b <i>Fusobacterium</i> spp. <i>Peptostreptococcus</i> spp. <i>Prevotella</i> spp. <i>Porphyromonas</i> spp.	Intravenous ampicillin–sulbactam Intravenous cefoxitin

^aDicloxacillin, cephalexin, erythromycin, and clindamycin have poor coverage against *Pasteurella multocida*. ^b*Eikenella corrodens* is resistant to first-generation cephalosporins, macrolides, clindamycin, and aminoglycosides.

as appropriate. If rabies is a concern, vaccination and immunoglobulin should be administered. For human bites, consider hepatitis B vaccination if needed and HIV postexposure prophylaxis if the patient is at high risk.

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Suggested Readings

Calliano C. Bedbugs (*Cimex lectularius*): identifying and managing an infestation. *Nurse Pract.* 2012;10:6-10.

Dendle C, Looke D. Management of mammalian bites. *Aust Fam Physician.* 2009;38:868-874.

Diaz, JH. The evolving global epidemiology, syndromic classification, management, and prevention of caterpillar envenoming. *Am J Trop Med Hyg.* 2005;72:347-357.

Ellis AK, Day JH. Diagnosis and management of anaphylaxis. *CMAJ.* 2003;169:307-311.

Golden DB, Moffitt J, Nicklas RA, et al. Stinging insect hypersensitivity: a practice parameter update 2011. *J Allergy Clin Immunol.* 2011;127:852-854.

Haddad V, Cardoso J, Lupi O, et al. Tropical dermatology: venomous arthropods and human skin: Part I. Insecta. *J Am Acad Dermatol.* 2012;67(3):331.e1-331.e14.

Haddad V, Cardoso J, Lupi O, et al. Tropical dermatology: venomous arthropods and human skin: Part II. Diplopoda, Chilopoda, and Arachnida. *J Am Acad Dermatol.* 2012;67(3):347.e1-347.e9.

Hossler EW. Caterpillars and moths. *Dermatol Ther.* 2009;22:353-366.

Lavonas EJ, Ruh AM, Banner W, et al. Unified treatment algorithm for the management of crotaline snakebite in the United States: results of an evidence-informed consensus workshop. *BMC Emerg Med.* 2011;11:2.

- Liberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol*. 2010;126:477-480.
- McClain D, Dana AN, Goldenberg G. Mite infestations. *Dermatol Ther*. 2009;22:327-346.
- Perkins RA, Morgan SS. Poisoning, envenomation, and trauma from marine creatures. *Am Fam Physician*. 2004;69:885-890.
- Rhoads J. Epidemiology of the brown recluse spider bite. *J Am Acad Nurse Pract*. 2007;19:79-85.
- Stevens DL, Bisno AL, Chambers HF. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis*. 2005;41:1373-1406.
- Weinstein S, Dart R, Staples A, White J. Envenomations: an overview of clinical toxicology for the primary care physician. *Am Fam Physician*. 2009;80:793-802.

I. BACKGROUND In the United States, approximately 450,000 individuals are treated for thermal injuries yearly, of whom 5,000 are hospitalized, 25,000 are admitted to specialized burn centers, and 3,500 die. Scalding by hot objects or liquids is most often the mechanism of injury in children, accounting for nearly 80% of burns, whereas flame burns are the most common mechanisms overall, with adults accounting for the majority. In fact, according to the Center for Disease Control, unintentional burns in patients from <1 to 4 years old continue to be one of the leaders in nonfatal injuries treated in US emergency departments yearly. Other possible burn etiologies include contact, chemical, electrical, radiation, and intentional burns. Contact burns predominate in the pediatric population in the home setting, whereas chemical and electrical burns are mostly attributed to industrial and workplace mishaps in the adult sector.

Sustained cutaneous exposure to temperatures exceeding 40°C has been shown to denature proteins and compromise plasma membrane integrity, resulting in thermal burns. The resultant degree of cutaneous damage is directly related to the duration and intensity of heat exposure, the type of heat source, and the thickness of the exposed cutaneous surface. Further, duration and intensity of the heat source are synergistic—coagulation necrosis results from 45°C exposure for 3,600 seconds or a 60°C exposure for 10 seconds. Both structural malformations and synthesis of local mediators such as histamine, serotonin, bradykinin, nitric oxide, and oxygen-free radicals contribute to the physiologic effects inherent in burn pathology. In addition to local changes, more systemic effects may ensue, manifesting as shock, respiratory and renal failure, cardiac depression, immunodeficiency, and the entrance into a hypermetabolic state where nutritional support becomes critical.

Burn categories are based on depth and are traditionally categorized as first, second, or third degree. The depth of the burn is often related to its cause. Scalds from hot liquids are usually partial thickness, whereas injuries from contact with flames, hot metal, or electric current are usually full thickness. However, thermal injuries are a dynamic entity, with the depth of the burn evolving over time and peaking at about 3 days, a process known as conversion. Therefore, it is often difficult to ascertain the true depth of injury at the time of presentation, presenting clear clinical challenges.

II. CLINICAL PRESENTATION First-degree burns involve only the epidermis and typically resemble a sunburn. The lesions are usually erythematous, edematous, painful, and dry. Desquamation may occur after a few days. These lesions usually heal within 5 to 10 days with postinflammatory pigmentary alteration but without scarring unless secondarily infected. Second-degree burns can be either superficial or deep. The former involves the entire epidermis and part of the underlying dermis, with patients displaying

blanchable erythema, edema, serous or hemorrhagic bullae, erosion, and exudation. The latter involves yet deeper layers of the dermis, with patients presenting with red to pale skin with serosanguineous or hemorrhagic bullae, erosions, and generally nonblanchable lesions. Superficial second-degree burns reepithelialize from adnexal structures (hair follicles) and, if left undisturbed, heal within 2 weeks without scarring. Deep second-degree burns often have damaged adnexal structures; healing rarely occurs within 3 weeks, with resultant scarring and contractures, especially in children. Third-degree burns involve the complete destruction of the epidermis and dermis, including the subcutaneous fat. The cutaneous surface may either assume a dry, firm, nonblanching, translucent appearance, often resembling parchment paper, or an anesthetic, charred, tan appearance with a leathery consistency. Such burns heal slowly, often over months, with hypertrophic scarring and contractures. First- and second-degree burns are generally painful, whereas destruction of the dermal plexus of nerves in third-degree burns renders the tissue insensitive to pain (Table 7-1).

III. WORKUP Factors that determine burn severity include total body surface area (TBSA) involvement (only second- and third-degree burns), depth of the injury, age, associated injuries, delay in resuscitation, and use of drugs, among others. Although a simplified approximation, the Rule of Nines is a quick and useful technique in assessing TBSA in adults (Fig. 7-1). Adjustments must be made for children under 10 years of age. Approximating the palmar hand surface as 1% TBSA may be used in this patient population. The depth of the burn and additional injuries are directly proportional to the severity. Mortality for a given burn size is directly proportional to the age. Delayed resuscitation efforts negatively dictate treatment options, and the use of drugs hinders resuscitation efforts greatly.

TABLE 7-1 **Severity of Burns**

First-degree burn (epidermal involvement)

Epidermis. Loss of intercellular cohesiveness with cleft formation

Dermis. Vasodilatation and edema

Second-degree burn (epidermal and partial dermal involvement)

Epidermis. Coagulative necrosis with bulla formation at dermoepidermal junction

Dermis. Marked vasodilatation and edema; destruction of adnexae may occur; evidence of continued capillary circulation may be observed

Third-degree burn (full-thickness burn)

Epidermis. Full-thickness coagulative necrosis of epidermis

Dermis. Variable dermal necrosis with destruction of adnexae

Subcutaneous tissue. Variable destruction/necrosis of subcutaneous tissue and adnexae

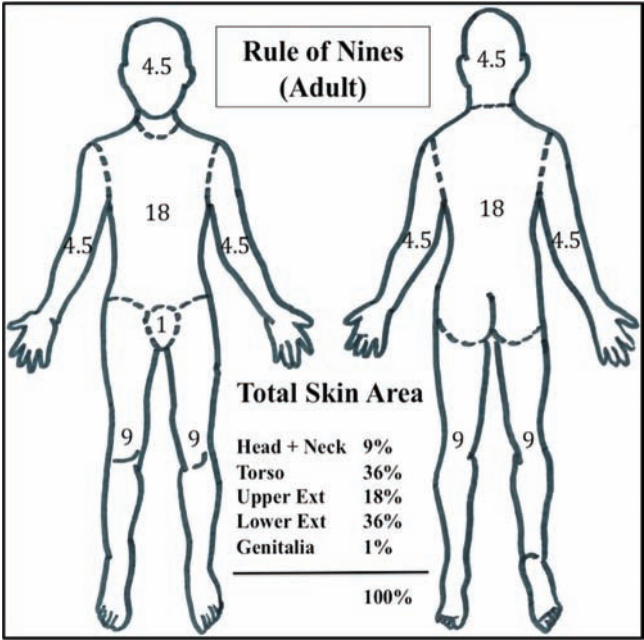


Figure 7-1. The “Rule of Nines” to assess total body surface area.

Initial assessment of patients with burns involving the head and neck should always include an airway evaluation due to the heightened risk for inhalation injury. Other important aspects that will guide future care—inpatient versus outpatient management—include the size, depth, and circumference of the burn. The evaluator should never fail to consider abuse as a possibility, especially in the pediatric and geriatric populations. Partial-thickness burns that involve <15% of TBSA and spare the face, hands, feet, and perineum or full-thickness burns of <2% of the body surface are classified as minor burns. Such burns can often be managed in an ambulatory setting. Second-degree burns involving <5% of the total TBSA and third-degree burns affecting <1% of TBSA in children may also be managed as an outpatient. Laser Doppler imaging is the latest innovation allowing exquisite assessment of true depth of injury and is a viable option for physicians in the hospital setting. Treatment should be dictated by the deepest depth present. Also, physicians may use the American Burn Association Burn Unit Referral Criteria for guidance on when patients should be referred to burn specialists (Table 7-2).

IV. TREATMENT The pathophysiology and therapy of moderate and severe burns will not be discussed. Such burns require intensive specialized care in hospitals to manage the wound and the cardiopulmonary disturbances caused by fluid and electrolyte changes associated with extensive cutaneous damage.

TABLE 7-2 Burn Center Referral Criteria^a

1. Partial-thickness burns >10% TBSA
2. Burns involving face, hands, feet, genitalia, perineum, or major joints
3. Third-degree burns (any age group)
4. Electrical burns, including lightning
5. Chemical burns
6. Inhalation injury
7. Burn injury in patients with underlying medical conditions that could complicate management, prolong recovery, or affect mortality
8. Any patient with burns and concomitant trauma (such as fractures) in which the burn injury poses the greatest risk of morbidity or mortality
9. Burned children in hospitals without qualified personnel/equipment for care of children
10. Burn injury in patients who will require special social, emotional, or rehabilitative intervention

^aExcerpted from Guidelines for the Operation of Burn Centers (pp. 79-86), Resources for Optimal Care of the Injured Patient 2006, Committee on Trauma, American College of Surgeons.

A. Initial Therapy

1. **Cool Running Water or Cool Compress.** Treatment of less severe burns should be started immediately with cool running water (15°C to 25°C). Cooling is an effective therapy because burnt skin still retains enough heat to extend coagulation to surrounding tissues. Also, cooling is thought to inhibit conversion of the injury (see the “Background” section). This is generally regarded as an acceptable preambulatory option, as it relieves pain quickly and temporarily, and reduces edema, reactive hyperemia, scarring, and mortality. Ice and ice water immersion should be avoided, as it can convert superficial partial-thickness burns into deeper burns and also precipitate hypothermia. Warm blankets may be used to cover uninjured areas to prevent hypothermia.

B. Continued Therapy

1. **First-Degree Burns.** The most superficial burns may require no dressing or medications, although the application of an emollient such as petrolatum or aloe vera may be soothing. Adequate pain management is a necessity, and can be sufficiently addressed with nonsteroidal anti-inflammatory drug. Although they lessen pain, topical anesthetics such as benzocaine add the risk of allergic contact dermatitis and are normally contraindicated.
2. **Second-Degree Burns.** Careful examination is necessary. Tetanus prophylaxis is normally indicated in all patients with greater than a first-degree burn. However, prophylactic systemic antibiotics are not recommended in general. A thorough cleansing of the wound can be accomplished with sterile water or saline. The use of an additional cleaning agent such as chlorhexidine is contraindicated. Deeper burns

require debridement of necrotic tissue. However, caution must be exercised, as it may be difficult to delineate the extent of the damage for 2 to 4 days thereafter. Debridement performed too early may remove living tissue. Traditionally, topical antibiotics, such as silver sulfadiazine (Silvadene) and mafenide acetate (Sulfamylon), have been used for broad-spectrum antimicrobial coverage and encouraged wound healing. However, studies have illustrated numerous toxicities, including transient leukopenia and metabolic acidosis, respectively. Xeroform, a nonabsorptive, occlusive dressing, is advantageous for dry burns due to comparative comfort, convenience, and compliance. If desired, the benefits of silver can be acquired through the use of silver-impregnated dressings such as Acticoat that utilize a slow-release mechanism. If oozing or weeping is present, application of an absorptive dressing, such as hydrocolloids (i.e., DuoDerm) or hydrogels (i.e., Aquasorb), will reduce pain and create a proper healing milieu simultaneously. Dressings should remain in place for several days unless there is copious exudate, in which case they need to be changed more often. Adherent dressings should be moistened, or the affected cutaneous surface should be bathed in warm water before the dressings are removed to ease removal and limit trauma. A burn specialist should be consulted before applying newer skin substitutes, such as the synthetic bilaminate biocomposite of nylon mesh bonded to silicon film membrane (Biobrane) and the fibroblast-derived polymer membrane (Transcyte). Despite growing evidence to the contrary, topical antibiotic agents such as silver sulfadiazine remain as common adjuncts in the treatment of second-degree burns.

3. **Chemical Burns.** Time of exposure to the chemical is directly proportional to the amount of tissue destruction, and as such, immediate removal of both clothing and the substance is critical. Copious irrigation with water should follow, as the depth of the injury may be reduced by 2 to 4 hours or more of washing. However, it is necessary to note that patients subjected to said hydrotherapies are at increased risk for hypothermia. Further, some agents, such as phenol, dry lime, muriatic acid, and sulfuric acid, are either insoluble or produce considerable exothermy in water, which may lead to further injury. Therefore, the specific therapy should be implemented and managed accordingly. Industrial toxicity texts or burn specialists should be consulted regarding specific therapy for offending chemicals.
4. **Rehabilitation.** Rehabilitation of burn patients may require years of therapy and depend heavily upon the associated sequelae present. Long-term, multidisciplinary management may require addressing the following complications, including but not limited to:
 - Blister formation
 - Infections by *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Acinetobacter*, and *Klebsiella* species
 - Pruritus
 - Neuropathy
 - Photosensitivity
 - Hypertrophic scar formation and secondary development of skin cancer, specifically squamous cell carcinoma
 - Psychiatric disorder (axis I or II) and psychosocial implications

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Suggested Readings

- Evers LH, Bhavsar D, Mailander P. The biology of burn injury. *Exp Derm*. 2010;19:777-783.
- Kramer CB, Rivara FP, Klein MB. Variations in US pediatric burn injury hospitalizations using the national burn repository data. *J Burn Care Res*. 2010;31(5):734-739.
- Lloyd EC, Rodgers BC, Michener M, Williams MS. Outpatient burns: prevention and care. *Am Fam Physician*. 2012;85(1):25-32.
- Palao R, Monge I, Ruiz M, Barret JP. Chemical burns: pathophysiology and treatment. *Burns*. 2010;36(3):295-304.
- Singer AJ, Dagum AB. Current management of acute cutaneous wounds. *N Engl J Med*. 2008;359(10):1037-1046.
- Sun CF, Lv XX, Li YJ, et al. Epidemiological studies of electrical injuries in Shaanxi province of China: a retrospective report of 383 cases. *Burns*. 2012;38(4):568-572.
- US Department of Health and Human Services. Burn triage and treatment: thermal injuries. <http://www.remm.nlm.gov/burns.htm>. Accessed August 21, 2012.

I. BACKGROUND Corns and calluses are hyperkeratotic lesions that form as a result of persistent pressure or frictional forces at a particular skin site. While the foot is the most predisposed site of involvement, lesions may occur at any location subjected to excessive mechanical force. Characteristic sites may be seen in laborers, musicians, and athletes and may serve as an “occupational mark.” Examples include the “drummer’s digit” or the “pulling boat hands” of the crew team. Hyperkeratosis is a physiologic process intended to form a protective barrier against further soft-tissue damage. There is reactive proliferation of keratinocytes, leading to stratum corneum thickening. Lesions become pathologic only when they become painful or limit a patient’s function. In cases of severe peripheral neuropathy or vascular disease, such as that seen in diabetes, hyperkeratotic lesions may be a harbinger of ulceration.

There are both intrinsic and extrinsic factors that may contribute to the development of corns and calluses. Intrinsic factors include the presence of bony prominences or abnormal foot mechanics, either hereditary or acquired. This may lead to excessive mechanical force on a neighboring digit or unbalanced pressure on the sole of the foot. Extrinsic factors that predispose one to hyperkeratotic lesions include the use of poorly fitted or damaged footwear. Women who wear high-heeled shoes with a small toe box are particularly at risk. In the absence of anatomical deformity or inappropriate equipment use, high levels of activity, as in athletics and laboring professions, is also a frequent cause.

II. CLINICAL PRESENTATION Corns and calluses display slightly different clinical characteristics and often occur at different sites. The corn (heloma) is distinguished from the callus by its small size, well-circumscribed nature, and presence of a central core (Fig. 8-1). The central core is a keratin plug that presses into the dermis, frequently leading to pain. Corns have been historically classified as a hard corn (heloma durum) or a soft corn (heloma molle); many authorities prefer description based solely on the anatomical location. The hard corn is more common, and typically occurs on the dorsolateral aspect of the fifth toe or the dorsum of the interphalangeal joints of the lesser toes (Fig. 8-2). The soft corn occurs as a macerated, extremely painful lesion in the interdigital spaces, most often between the fourth and fifth toes. A breach in the epidermal barrier at this site predisposes to secondary fungal and bacterial infections, as well as underlying sinus formation. A “kissing lesion” is characterized by two opposing lesions within the same interdigital site.

The callus (tyloma, clavus) is identified by its large size and poorly circumscribed nature (Fig. 8-3). It characteristically lacks a central core and is of uniform thickness throughout. Depending on the location and severity, a callus may or may not elicit pain. It is most often found at sites of weight-bearing, which typically includes the heel and ball of the foot. Calluses are also often



Figure 8-1. This corn demonstrates the characteristic central core (*arrow*). (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 8-2. Typical location of corns on the dorsum of the interphalangeal joints of the lesser toes and dorsolateral aspect of the fifth toe. (From Berg D, Warzala K. *Atlas of Adult Physical Diagnosis*. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)



Figure 8-3. This callus, occurring over the fifth metatarsal head, demonstrates the characteristic maintenance of skin lines. (Courtesy of Julia A. Bloom, MD.)

found at the site of placement of musical instruments or at the location of repetitive friction during vigorous athletic activity.

The differential diagnosis for a corn or callus includes a verruca. Distinguishing features include the maintenance of dermatoglyphs (skin lines) overlying that of a callus, while these lines are obliterated in the presence of a verruca. Although dermatoglyphs may not be immediately evident overlying the corn, paring to a level below the central core will lead to the re-emergence of these lines. Furthermore, paring of a corn or callus often does not lead to bleeding; paring of the wart will often result in the appearance of central red and black dots (thrombosed arteries) and punctate bleeding due to its highly vascularized nature. Pain is elicited most readily with lateral pressure on a wart, while direct pressure causes greatest pain in a corn.

III. WORKUP The evaluation for a hyperkeratotic lesion includes a thorough history and physical examination. The patient should be asked about occupation, athletic pursuits, or hobbies that may contribute to excessive mechanical force at the involved site. A knowledge of underlying disease states such as diabetes and rheumatoid arthritis may help direct further assessment and treatment. A full anatomic assessment of the affected site should be completed, which may include radiologic imaging to evaluate for an underlying bony deformity. If suspicion exists for underlying peripheral neuropathy, a thorough evaluation of sensory and motor function should be done. Gait assessment should also be performed to assess for signs such as shuffling and uneven stepping.

TABLE 8-1 Primary Treatment Options for Corns and Calluses

1. Surgical debridement
2. Keratolytic agents
3. Foot orthoses

IV. TREATMENT The treatment of corns and calluses includes strategies aimed at debriding the lesion and minimizing further mechanical stress to the affected site (Table 8-1). For diabetic patients, prompt recognition and management of corns and calluses are paramount to avoid future ulceration.

A. Debridement

1. **Sharp Debridement.** A curette, scalpel (e.g., 15-blade), or chisel blade may be used to pare down the lesion. For a corn, special attention must be placed on removal of the central core, which often requires local anesthesia.
2. **Maintenance Debridement.** The patient should be instructed to perform regular home debridement to help prevent recurrence.
 - a. **Warm Water Soaks.** Soak the lesion in warm water for ~20 minutes, followed by gentle paring with a pumice stone or emery board.
 - b. **Keratolytic agents.** The use of dilute keratolytic agents (10% to 15% salicylic acid) may be beneficial. Caution should be used when using higher concentrations, given the concern for damage to the surrounding normal skin. Salicylic acid plaster (40%) can be used by cutting a piece only slightly larger than the size of the lesion and left on overnight; tape may be used to secure the dressing. The dressing is then removed in the morning, followed by gentle paring (as noted above) of the macerated skin. This can be repeated for 5 to 7 days and then intermittently to ensure the lesion remains flat. In diabetic patients, it is important to maintain hydration in the feet with humectant agents, such as urea cream and 12% ammonium lactate. Low concentration urea creams (10% to 15%) are effective in moisturizing, while higher concentrations (20% to 40%) may display keratolytic effects.
3. **Intralesional Steroid Injection.** While not universally advocated, the use of intralesional steroid (e.g., Kenalog) may be used to flatten the lesion.

B. Addressing and Modifying the Mechanical Etiology

1. **Orthoses**
 - a. **Cushioning Products.** Lamb's wool, silicone sleeves, metatarsal pads, and cushioning insoles may help off-load pressure from the affected site.
 - b. **Toe Spacers.** May be utilized in the setting of an interdigital corn to relieve pressure from the neighboring toe.
2. **Footwear.** Depending on the site of lesion involvement, shoes should be chosen with low-heels, soft upper, wide toe box, plantar cushioning, and ample stretching capacity.
3. **Surgery.** May be considered in recalcitrant cases and may include condylectomy or other surgical techniques aimed at correcting a specific foot deformity.

4. **Fillers.** Controversial treatment modality; variable success has been achieved through the use of subcutaneous injection of filler substances underlying the site of involvement.

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Suggested Readings

- Bryant JL, Beinlich NR. Foot care: focus on the elderly. *Orthop Nurs*. 1999;18:53-60.
- Freeman DB. Corns and calluses resulting from mechanical hyperkeratosis. *Am Fam Physician*. 2002;65:2277-2280.
- Gambichler T, Boms S, Freitag M. Contact dermatitis and other skin conditions in instrumental musicians. *BMC Dermatol*. 2004;4:3.
- Pavicic T, Korting HC. Xerosis and callus formation as a key to the diabetic foot syndrome: dermatologic view of the problem and its management. *J Dtsch Dermatol Ges*. 2006;4:935-941.
- Singh D, Bentley G, Trevino SG. Callosities, corns, and calluses. *BMJ*. 1996;312:1403-1406.
- Smith BW, Coughlin MJ. Disorders of the lesser toes. *Sports Med Arthrosc*. 2009;17:167-174.

ATOPIC DERMATITIS/ECZEMA

I. BACKGROUND Atopic dermatitis (AD) is an intensely pruritic, chronic skin disease that can affect all age groups, but usually arises within the first 5 years of life. AD can be classified into three stages: infantile, childhood, and adulthood. The infantile form tends to be highly inflammatory and favors the face and the extensor surfaces. The adulthood form tends to show low-grade inflammation and marked lichenification and favors the flexural surfaces. The childhood form can show features of both the infantile and the adulthood form, but with time will progress to favor the adulthood form.

AD is a common condition with an estimated prevalence of 10% to 20% in American schoolchildren. Increased frequencies of AD are seen in individuals with parental history of atopy; however, the environment also seems to play a role in the development of AD. Specifically, individuals within highly industrialized societies and advantaged socioeconomic classes are at an increased risk for developing AD. The pathogenesis of AD is highly multifactorial and not completely understood. It is generally agreed, however, that AD is related to immunologic abnormalities, compromised skin barrier function, blood vessel reactivity, and abnormalities in cutaneous nerves and neuropeptides. Notable immunologic abnormalities include activation of the T-helper 2 response, elevated serum immunoglobulin E levels, peripheral blood eosinophilia, and abnormally exuberant immune reactions to various antigens including allergens and microbial agents. Individuals with AD not only have exuberant reactions to microbial agents but also have increased susceptibility to microbial agents. It is estimated that over 90% of AD lesions are colonized with microbial agents, most commonly with *Staphylococcus aureus* (*S. aureus*). This increased susceptibility is attributed not only to the compromised skin barrier but also to the reduced expression of antimicrobial peptides seen in AD.

II. CLINICAL PRESENTATION All forms of AD share the feature of intense pruritus and xerosis in a relapsing and remitting course. The pruritus is often worse in the evening and can be exacerbated by heat, sweating, and contact with wool clothing. It is the scratching and rubbing resulting from this pruritus, which typically initiates the formation of the classic AD skin lesions. Xerosis is seen in the majority of individuals with AD and generally involves the entire skin surface, not only areas affected by dermatitis.

The infantile form usually presents in the first 2 to 12 months of life and is characterized by intensely pruritic, brightly erythematous papules and plaques. These lesions often have overlying vesicles, oozing, serous crusting, and secondary excoriations and are distributed over the face (especially the cheeks), scalp, and extensor surfaces (Fig. 9-1). The diaper area is classically spared.



Figure 9-1. Atopic dermatitis, infantile form. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

The childhood form defines AD in individuals between 2 and 12 years of age. The clinical features usually resemble the infantile form early on and over time evolve toward the adulthood form. The adulthood form is characterized by subacute to chronic lesions with increased scale and lichenification and decreased erythema, vesiculation, oozing, and crusting (Fig. 9-2). The lesions favor the flexural areas including the neck, antecubital fossa, and popliteal fossa, but can also commonly involve the hands and eyelids. Additional features commonly associated with AD are listed in Table 9-1.

The most common complication seen in the setting of AD is secondary infection. The most common agent causing secondary infection is *S. aureus*. It should be suspected when the AD lesions show prominent crusting and oozing. Treatment with antistaphylococcal antibiotics with good skin penetration is then indicated. Patients with AD are also predisposed to cutaneous viral infections, including warts, molluscum contagiosum, and herpes simplex virus (HSV). Infection of AD lesions with HSV presents with numerous monomorphic punched-out erosions or hemorrhagic crusts known as eczema herpeticum (Fig. 9-3).

III. WORKUP AD is a clinical diagnosis and typically no additional workup is needed. Features that support a diagnosis of AD include pruritus, involvement of flexural surfaces in children and adults, involvement of face and extensor



Figure 9-2. Atopic dermatitis, adult form. Note the flexural and hand involvement. (Courtesy of Esther K. Chung, MD.)

surfaces in infants, a personal or family history of asthma, seasonal allergies or AD, and a history of dry or sensitive skin. If the presentation is atypical, a skin biopsy can be performed; however, it is important to be aware that all forms of dermatitis, regardless of the cause, will show similar histologic features. Although questions regarding food allergens are often raised by patients or their

TABLE 9-1 Clinical Features Associated with Atopic Dermatitis	
Clinical Feature	Description
Keratosis pilaris	Horny plugs within hair follicle orifices favoring the lateral aspects of the upper arms and thighs in adults and the cheeks in children
Ichthyosis vulgaris	Autosomal dominant disorder due to a mutation in the filaggrin gene characterized by excessive fish-like scaling, especially over shins
Palmoplantar hyperlinearity	Increased prominence of palmar and plantar skin creases
Pityriasis alba	Poorly defined hypopigmented patches with fine scale most commonly on the face of children
Lichenification	Thickening of skin with exaggeration of skin markings from repeated rubbing
Dennie-Morgan lines	Symmetric fold(s) inferior to the lower eyelid margin extending from the medial canthus



Figure 9-3. Eczema herpeticum. Note the monomorphic punched-out erosions and crusting. (From Fleisher GR, Ludwig S, Baskin MN. *Atlas of Pediatric Emergency Medicine*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

families, food allergens are rarely associated with AD and such allergy testing is generally not advantageous. If there is a concern for secondary infection, appropriate cultures should be obtained.

IV. TREATMENT The treatment of AD should focus on good skin care, reducing any possible triggers and treating active flares as needed. The mainstay of good skin care is frequent use of emollients to increase skin hydration and barrier function. In general, ointments and creams will be more occlusive, and thus more effective, than their lotion counterparts. Creams containing ceramides can be especially useful as they replete the naturally occurring ceramides that are generally diminished in xerotic skin. Ideally, emollients should be applied within minutes of bathing or showering. Daily baths or shower is recommended; however, they should be limited to 10 minutes in length and hot water should be avoided. Fragrance-free soaps or soap-free cleansers specially formulated for dry or sensitive skin are also recommended. Possible triggers that should be avoided include fragrances, alkaline soaps, harsh chemicals, frequent hand washing, and dust mites. Treatment for active AD flares includes topical corticosteroids and calcineurin inhibitors, sedating antihistamines, antimicrobials for secondary infections, phototherapy, and systemic immunomodulating agents for especially recalcitrant disease (Table 9-2).

A. Topical Corticosteroids. Topical corticosteroids are generally considered first-line treatment for AD. While topical corticosteroids are safe when used properly, the risks of skin atrophy, glaucoma, cataracts, and systemic absorption should be reviewed with patients. It is important to remember that infants' increased body surface area to volume ratio makes them particularly susceptible to systemic absorption and thus higher potency agents should be used with extra caution in infants and young children.

TABLE 9-2 Primary Treatment Options for Atopic Dermatitis

1. Emollients
2. Topical corticosteroids
3. Topical calcineurin inhibitors
4. Sedating antihistamines
5. Antimicrobials PRN

Generally speaking, only low-potency topical steroids such as hydrocortisone and desonide should be used on the face and body folds to minimize the risk of complications. A medium potency topical steroid such as 0.1% triamcinolone is usually a good choice for the rest of the body. Thick, lichenified plaques or plaques on acral skin may require a more potent agent such as fluocinonide and clobetasol. For AD, ointments are generally preferred to creams, which in turn are preferred to lotions. Patients should be instructed to use the topical corticosteroid twice daily during flares, and then to taper off the medication as their symptoms improve.

- B. Topical Calcineurin Inhibitors (TCIs).** TCIs such as tacrolimus and pimecrolimus are useful steroid-sparing agents in the treatment of AD. As TCIs are not associated with skin atrophy and glaucoma or cataract formation, they are especially good treatment options for AD of the face (especially the periocular areas), neck, axilla, and groin.
- C. Sedating Antihistamines.** Antihistamines such as hydroxyzine, diphenhydramine, and doxepin can be useful for decreasing pruritus and thus any resulting scratching. Given their sedating nature, they are best used at bedtime and are especially helpful in patients whose itching interferes with their sleep.
- D. Antimicrobial Agents.** Antimicrobials should be administered when there is a concern for secondary infection. As *S. aureus* is the most common causative agent, cephalexin is often an effective choice. Prior to administering antibiotics, lesions should be cultured to monitor for the development of resistance. Monitoring for resistance is especially important in patients who require multiple antibiotic courses. Weekly or biweekly bleach baths, in which a ¼ to ½ cup of household bleach is poured into a full tub of water, are effective for reducing bacterial colonization and thus the risk of secondary infection. In the case of eczema herpeticum, treatment with IV or PO acyclovir or valacyclovir should be initiated immediately.
- E. Phototherapy.** Various forms of phototherapies have been shown to be effective for AD. The most commonly used form is narrowband UVB. Phototherapy is considered to have a favorable side-effect profile when compared with systemic immunomodulating agents; however, long-term risks include photoaging and increased risk of cutaneous malignancies.
- F. Systemic Immunomodulating Agents.** Systemic immunomodulating agents such as systemic corticosteroids, cyclosporine, methotrexate, mycophenolate mofetil, and azathioprine are generally reserved for the most recalcitrant cases of AD given their more concerning side-effect profile. If systemic immunomodulators are considered, a thorough discussion of risks and benefits must be held with the patient.

CONTACT DERMATITIS

I. BACKGROUND Contact dermatitis is a condition in which the skin becomes acutely inflamed due to direct contact with a substance. There are two forms of contact dermatitis, allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD). ICD is the more common of the two, accounting for 70% to 80% of all occupational skin disorders. Unlike ACD, ICD is not immunologically initiated, instead it results from direct cytotoxic effects of the irritant to the skin. Common causes of ICD include excessive wet work, detergents, acids, alkalis, oils, organic solvents, and other chemicals. As this reaction is nonallergic in nature, any person exposed to the offending agent may have a similar reaction, provided that the concentration and duration of contact are sufficient.

ACD is a delayed-type hypersensitivity reaction that is elicited when an individual comes into contact with a chemical to which he/she has previously been sensitized. Some of the most common causes of ACD include nickel, neomycin sulfate, balsam of Peru, fragrances, preservatives, adhesives, and poison ivy. The sequence leading to ACD starts when an individual first comes into contact with the chemical, thereby initiating a cascade of immunologic events that result in sensitization. On re-exposure to the chemical, primed T cells release inflammatory cytokines and chemotactic factors that result in the classic cutaneous manifestations of ACD, including erythema, edema, and pruritus.

II. CLINICAL PRESENTATION ACD and ICD can have very similar clinical presentations. In both cases, an eczematous eruption with well-demarcated margins corresponding to the area of contact is generally seen (Fig. 9-4). The presence of geometric lesions should raise the suspicion for a



Figure 9-4. Allergic contact dermatitis to the nickel snap on jeans. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 9-5. Allergic contact dermatitis to poison ivy. Note the linear streaks suggesting that it was an external agent (i.e., rubbing against a leaf) that caused the dermatitis. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

contact dermatitis, as this suggests that an external agent is responsible for the eruption (Fig. 9-5). Acutely, contact dermatitis will be brightly erythematous and edematous, but may also develop vesicles and scale. Chronic contact dermatitis will be less inflammatory and often show evidence of lichenification. While it is not always possible to distinguish between ACD and ICD, generally speaking ACD tends to be exquisitely pruritic, whereas ICD tends to be accompanied by a burning or stinging sensation.

III. WORKUP The diagnosis of contact dermatitis requires a careful history of possible contacts, including household, occupational, and recreational exposures. If a causative agent is clear from the history, this agent should be strictly avoided. If ACD is suspected, the gold standard for diagnosis is patch testing. Patch testing involves the direct application of potential allergens to

the skin and then monitoring for any reactions. If the clinical presentation is atypical, a skin biopsy can be performed; however, it is important to be aware that all forms of dermatitis, regardless of the cause, will show similar histologic features.

IV. TREATMENT The primary treatment for contact dermatitis is avoidance of the causative irritant or allergen. If the causative agent cannot be avoided, as in the case of an occupational allergen, personal protective equipment such as gloves, special clothing, and barrier creams should be utilized. Acute contact dermatitis can be treated with topical or systemic corticosteroids, depending on the severity of the reaction. However, it is important to educate the patient that treatment with corticosteroids will not be effective if the patient continues to be exposed to the causative agent. Patients should also be educated on good dry skin care, including the use of emollients, to maintain skin barrier function and thus lessen the risk of contact dermatitis (Table 9-3).

LICHEN SIMPLEX CHRONICUS

I. BACKGROUND Lichen simplex chronicus (LSC) is a form of dermatitis that results from habitual rubbing and scratching of a localized area of skin. The urge to scratch may have had a clear trigger, such as a mosquito bite, or may be linked to stress, anxiety, or habit. When skin is exposed to such trauma, the skin becomes thickened and leathery. The skin markings oftentimes become more prominent and the skin color may darken. These changes are known as lichenification. The more a lichenified area is scratched or rubbed, the more pruritic it becomes, thereby promoting an itch–scratch–itch cycle. This cycle can be very difficult to break, especially since scratching these areas often times becomes a highly pleasurable activity for the affected individual.

II. CLINICAL PRESENTATION LSC presents with well-circumscribed plaques of thickened skin with prominent skin markings (Fig. 9-6). Sometimes these plaques will have overlying excoriations or fine scale. LSC has a predilection for the posterior neck, scalp, ankles, wrists, vulva, scrotum, and anal area, but can occur at any site.

III. WORKUP LSC is a clinical diagnosis and generally no further workup is indicated. If the presentation is atypical, the diagnosis can be confirmed with a skin biopsy. It is important to remember that lichenification can be seen as a secondary change to a variety of other primary diseases, including AD, contact dermatitis, stasis dermatitis, and tinea. Thus, it is crucial to exclude an underlying primary disease, as such patients would benefit from directed therapy.

TABLE 9-3	Primary Treatment Options for Contact Dermatitis
<ol style="list-style-type: none">1. Avoidance of a causative agent2. Topical or systemic corticosteroids3. Emollients	



Figure 9-6. Lichen simplex chronicus. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

TABLE 9-4	Primary Treatment Options for Lichen Simplex Chronicus
<ol style="list-style-type: none"> 1. Avoidance of scratching or rubbing 2. Topical or intralesional corticosteroids 3. Complete occlusion (Unna boot) 	

IV. TREATMENT Treatment of LSC focuses on breaking the itch–scratch–itch cycle. The patient should be educated on the importance of not scratching and informed that the sensation of itch will decline over time. High-potency topical corticosteroids can be used initially to decrease pruritus, but should be avoided as chronic therapy given the risk of atrophy. In some cases, intralesional injections of 5 mg/mL triamcinolone suspension may also be useful. In severe cases, placement of an Unna boot may force the patient to stop scratching and thus break the cycle (Table 9-4).

Suggested Readings

Huang JT, Abrams M, Tlougan B, Rademaker A, Paller AS. Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity. *Pediatrics*. 2009;123(5):e808-e814.

Lipozencic J, Wolf R. The diagnostic value of atopy patch testing and prick testing in atopic dermatitis: facts and controversies. *Clin Dermatol*. 2010;28:38-44.

Mowad CM. Patch testing: pitfalls and performance. *Curr Opin Allergy Clin Immunol*. 2006;6:340-344.

Shams K, Grindlay DJ, Williams HC. What's new in atopic eczema? An analysis of systematic reviews published in 2009–2010. *Clin Exp Dermatol*. 2011;36: 573-577 (quiz 577-578).

I. BACKGROUND A dermatofibroma (benign fibrous histiocytoma) is a benign growth of dermal fibroblasts. Dermatofibromas are common and are often overlooked by patients as they mimic nevi and other benign skin growths. Their cause is unknown, but they are thought to arise from an antecedent arthropod bite, folliculitis, trauma, or other inflammatory insult. Multiple dermatofibromas may occur in association with lupus or immunosuppression.

II. CLINICAL PRESENTATION Dermatofibromas most frequently occur in young- to middle-aged adults and are more common in women. They are typically located on exposed areas of the extremities, especially the legs, but can occur on the torso and the head. Although often asymptomatic there can be associated pruritus or pain, and they typically do not continue to grow after reaching a stable size. Prior history of trauma or arthropod bite in the area may be reported by the patient but is not required for the diagnosis.

Physical examination of a dermatofibroma is often diagnostic and reveals a very firm, brown to red-brown, <1 cm, round papule or nodule (Fig. 10-1). Uncommon variants include multiple clustered dermatofibromas in children, and a giant dermatofibroma mimicking a malignant tumor. As dermatofibromas are frequently hyperpigmented, they can be confused with more concerning pigmented lesions such as atypical nevi and melanoma (Fig. 10-2). Clues to help the clinician differentiate dermatofibromas from other lesions include the firmness of the lesion upon palpation, the “dimple” sign (Fig. 10-3), and a typical dermoscopic pattern of a central white patch with peripheral pigment network. Infrequently overlying sebaceous hyperplasia may be noted, and if located in an atypical site for sebaceous glands, this can be a clue to the diagnosis of dermatofibroma.¹

III. WORKUP Because of their distinctive clinical features, dermatofibromas can be diagnosed clinically. For lesions showing atypical features, such as persistent growth, biopsy is indicated. Punch, excisional, or shave biopsy are all appropriate techniques. However, a superficial shave biopsy may only show nonspecific epidermal changes. Furthermore, patients should be informed that the scar after even a small biopsy may be larger and more prominent than the original lesion. These lesions may recur after biopsy or excision. Histopathology typically demonstrates a poorly defined spindle cell proliferation in the dermis with surrounding collagen trapping and overlying epidermal hyperplasia. Factor XIIIa positivity and CD34 negativity can help distinguish dermatofibroma from dermatofibrosarcoma protuberans (DFSP). Histologic variants demonstrating monster cells, vascularity, and deeper subcutaneous extension can occur.



Figure 10-1. Dermatofibroma. The lesion in this patient is typical: a firm, sharply outlined reddish-brown nodule. (From McConnell TH. *The Nature of Disease Pathology for the Health Professions*. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.)



Figure 10-2. Pigmented dermatofibroma. Palpation and dermoscopy can help to differentiate from other pigmented lesions.



Figure 10-3. The “dimple” sign. Central depression noted upon pinching of the skin around the lesion. (From Goodheart HP. *Goodheart’s Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

The differential diagnosis includes nevus, cyst, DFSP, adnexal tumor, squamous cell carcinoma, and melanoma (Table 10-1).

IV. TREATMENT Because of their benign nature, typical dermatofibromas do not require treatment. Patients often request treatment due to symptoms or for cosmesis, and consideration of the risks and benefits should accompany any discussion of treatments for this benign growth.

A. Surgical Excision. Excision of the dermatofibroma is the most definitive treatment, but patients should be cautioned that the scar from

TABLE 10-1	Differential Diagnosis for Dermatofibroma
<ul style="list-style-type: none">• Nevus• Cyst• Melanoma• Dermatofibrosarcoma protuberans• Adnexal tumor	
Primary Treatment Options	
<ol style="list-style-type: none">1. Surgical excision2. Cryotherapy3. Pulsed-dye laser	

dermatofibroma excision is typically larger and more noticeable than the original lesion. Prior to excision, the lesion should be palpated to determine the extent of the lesion. Excision is performed in a fusiform fashion down into the subcutaneous fat to include a small margin, typically 1 to 2 mm, of normal skin beyond the palpable border of the lesion. The specimen should be sent for pathologic examination and confirmation of the diagnosis.

- B. Cryotherapy.** Cryotherapy carries a lower risk of scarring than surgery but may still be an efficacious treatment option for dermatofibromas. Treatment typically consists of a 30-second spray of liquid nitrogen applied to the lesion and 2 mm of surrounding normal-appearing skin. Raised lesions can be shaved flat prior to application of liquid nitrogen to increase penetration of treatment. Treatments can be repeated every 1 to 2 months as needed. The patient should be warned of possible side effects of blistering, crusting, and discomfort. The hypopigmentation that can occur after cryotherapy is often a desired side effect in the treatment of hyperpigmented dermatofibromas, but its potential should be discussed especially with darker skinned patients. Although complete resolution or >50% improvement in size and appearance was noted in >90% of patients by one author,² many do not see such a clinical improvement.
- C. Pulsed-Dye Laser.** More recently, pulsed-dye laser has been described as an effective treatment for dermatofibromas that also carries a potentially better cosmetic outcome than surgery. Although there are no established guidelines, one author noted improvement in a majority of patients after two to three stacked pulses with a 595-nm wavelength pulsed-dye laser using a 7-mm spot size, 2-ms pulse duration, and fluence of 11 J/cm².³

REFERENCES

1. Fuciarelli K, Cohen PR. Sebaceous hyperplasia: a clue to the diagnosis of dermatofibroma. *J Am Acad Dermatol.* 2001;44(1):94-95.
2. Lanigan SW, Robinson TW. Cryotherapy for dermatofibromas. *Clin Exp Dermatol.* 1987;12(2):121-123.
3. Alonso-Castro L, Boixeda P, Segura-Palacios JM, de Daniel-Rodríguez C, Jiménez-Gómez N, Ballester-Martínez A. Dermatofibromas treated with pulsed dye laser: clinical and dermoscopic outcomes. *J Cosmet Laser Ther.* 2012;14(2):98-101.

Suggested Readings

- Han TY, Chang HS, Lee JH, Lee WM, Son SJ. A clinical and histopathological study of 122 cases of dermatofibroma (benign fibrous histiocytoma). *Ann Dermatol.* 2011;23(2):185-192.
- Zaballos P, Puig S, Llambrich A, Malvehy J. Dermoscopy of dermatofibromas: a prospective morphological study of 412 cases. *Arch Dermatol.* 2008;144(1):75-83.

11

Diaper Dermatitis

Pamela Chayavichitsilp

- I. BACKGROUND** Diaper dermatitis is a form of irritant contact dermatitis that is common in the pediatric population. It can present as early as 3 weeks of age or as late as 2 years old.
- II. CLINICAL PRESENTATION** Diaper dermatitis presents as erythema and mild scaling on the convex surfaces of the medial thigh, lower abdomen, and buttock, classically sparing the inguinal folds where the skin is not in contact with irritants (Fig. 11-1). The irritants, typically urine and feces, create moisture and increased pH which compromise skin integrity. The reduction in skin barrier function further increases susceptibility to infections to microorganisms such as *Candida albicans*. These organisms further increase the clinical severity of diaper dermatitis.
- III. WORKUP** Many other dermatoses can affect the diaper area and need to be excluded. Skin cultures or KOH preparation can be performed to identify *C. albicans*, which is the most common infectious etiology of diaper dermatitis. A biopsy is usually not necessary, but can be performed to rule out other causes such as psoriasis, lichen sclerosis, and Langerhans cell histiocytosis. Patch testing may also be performed if allergic contact dermatitis is suspected. Common causes of allergic contact dermatitis include chemicals contained in baby wipes and diapers themselves, which tend to present in a pattern that resembles a cowboy's holster due to elastic bands coming into contact with the skin. If zinc deficiency is suspected, a zinc level should be obtained from a blood sample (Tables 11-1 and 11-2).
- IV. TREATMENT** Since diaper dermatitis is caused by irritants that lead to skin breakdown, management aims at preventing overhydration and frictional damage in the diaper area (Table 11-3).
- A. Frequent Diaper Changes**, particularly after defecation, reduce moisture and prevent the buildup of irritants. This is, therefore, one of the most important steps in the management of diaper dermatitis. Disposable diapers containing superabsorbent-gelling materials and breathable backsheets are preferred. Cloth diapers should be avoided, as they have been shown to be associated with an increased incidence of diaper dermatitis compared with disposable diapers.
 - B. The Skin in the Area May Be Cleaned with Water Alone or with Mild Soap.** Baby wipes should not contain fragrance or alcohol. Rubbing of the area can cause damage to the skin and should be avoided.
 - C. A Barrier Cream** may be applied at every diaper change. Examples of readily available preparations include Desitin and Dr. Smith's. This can



Figure 11-1. Classic diaper dermatitis in an infant affecting the convex surfaces that come into contact with irritants. (Courtesy of Lawrence F. Eichenfield, MD.)

TABLE 11-1	Differential Diagnosis
Noninfectious	
• Allergic contact dermatitis	
• Psoriasis	
• Zinc deficiency	
• Lichen sclerosus	
• Miliaria rubra	
• Langerhans cell histiocytosis	
Infectious	
• <i>Candida albicans</i>	
• Group A β -hemolytic <i>Streptococcus</i>	
• <i>Staphylococcus</i> spp.	
• Herpes simplex virus	
• Molluscum	
• Enterovirus (hand, foot, and mouth disease)	

TABLE 11-2	Laboratory Workup (If Indicated)
<ul style="list-style-type: none">• KOH preparation• Fungal culture• Bacterial culture• Zinc level• Skin biopsy• Patch testing	

TABLE 11-3	Primary Treatment Options
<ol style="list-style-type: none">1. Frequent diaper changes2. Clean area with water and mild soap3. Barrier creams4. Mild corticosteroid (1% hydrocortisone ointment)5. Topical antifungal agent (miconazole, clotrimazole, nystatin, ketoconazole)	

provide a barrier between the skin and irritants in order to reduce friction and contact with stool and urine.

D. A Low-Potency Topical Steroid such as hydrocortisone 1% ointment can be applied for a short time in more severe cases of diaper dermatitis, but must be used sparingly to avoid skin atrophy and systemic absorption. Avoid the use of high-potency steroids, including compound formulations containing potent steroids and antimicrobial agents.

E. Topical Antifungal Preparations are recommended for use in proven or suspected cases of *C. albicans* infection. Some commonly used antifungals include miconazole, clotrimazole, nystatin, and ketoconazole.

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Suggested Readings

Baldwin S, Odio MR, Haines SL, O'Connor RJ, Englehart JS, Lane AT. Skin benefits from continuous topical administration of a zinc oxide/petrolatum formulation by a novel disposable diaper. *J Eur Acad Dermatol Venereol.* 2001;1:5-11.

Eichenfield LF, Bogen ML. Absorption and efficacy of miconazole nitrate 0.25% ointment in infants with diaper dermatitis. *J Drugs Dermatol.* 2007;6:522-526.

Hoeger PH, Stark S, Jost G. Efficacy and safety of two different antifungal pastes in infants with diaper dermatitis: a randomized, controlled study. *J Eur Acad Dermatol Venereol.* 2010;24(9):1094-1098.

- Odio M, Friedlander SF. Diaper dermatitis and advances in diaper technology. *Curr Opin Pediatr*. 2000;12:342-346.
- Railan D, Wilson JK, Feldman SR, Fleischer AB. Pediatricians who prescribe clotrimazole-betamethasone dipropionate (Lotrisone) often utilize it in inappropriate settings regardless of their knowledge of the drug's potency. *Dermatol Online J*. 2002;8:3.
- Ravanfar P, Wallace JS, Pace NC. Diaper dermatitis: a review and update. *Curr Opin Pediatr*. 2012;24:427-479.
- Smith WJ, Jacob SE. The role of allergic contact dermatitis in diaper dermatitis. *Pediatr Dermatol*. 2009;26(3):369-370.

I. BACKGROUND Cutaneous adverse drug eruptions (CADEs) may occur on an immunologic or a nonimmunologic basis. Of all adverse drug reactions (ADRs), nonimmunologic ADRs outnumber immunologic drug reactions. However, with regard to cutaneous adverse reactions, an immunologic etiology should be suspected. Important exceptions are pseudoallergic reactions, which are caused by direct mast cell release, complement activation, or alteration of arachidonic acid metabolism, clinically mimicking a true allergy. Common etiologic agents of pseudoallergic reactions include opiates, aspirin, vancomycin, and radiocontrast media.

Hypersensitivity drug reactions may be grouped according to the Gell-Coombs classification:

1. **Type I**—immunoglobulin E (IgE)-dependent reactions (urticaria, angioedema, and anaphylaxis). Type I reactions may be immediate or may take >72 hours to occur.
2. **Type II**—cytotoxic reactions: antibody against a fixed antigen (drug-induced pemphigus and petechiae secondary to drug-induced thrombocytopenia).
3. **Type III**—immune-complex formation (vasculitis and serum sickness-like reaction [SSLR]).
4. **Type IV**—delayed-type hypersensitivity, cell-mediated mechanism exanthems, fixed drug eruption (FDE), lichenoid eruption, acute generalized exanthematous pustulosis (AGEP), erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS), and pseudolymphoma.

In a recent study, there were an estimated 635,982 CADE-related outpatient visits per year to United States outpatient clinics and emergency departments, with 2.26 CADEs per 1,000 persons. The incidence of CADEs increased with age, affecting ages 70 to 79 most significantly.¹ ADRs occur in 6.7% of all hospitalized patients, with cutaneous drug reactions occurring in >2% of hospitalized patients.²

II. CLINICAL PRESENTATION In addition to skin findings, drug reactions may be manifested as fever or as alterations of one or many organ systems (e.g., hemolysis, thrombocytopenia, and renal damage).

A. Exanthematous Eruptions

- The most common type of cutaneous reaction.
- Also described as morbilliform or maculopapular.
- Usually appear after 1-2 weeks of the causative drug being started; sensitization may occur after the first exposure or may develop to an antigen that the patient has been intermittently exposed to for years.

- A rash may also start within 4 to 7 days of the offending drug being stopped (some antibiotics, particularly semisynthetic penicillins and allopurinol, may produce a rash 2 or more weeks after initiation).
- Lesions most often start first and clear first from the head and upper extremities. Lesions of the trunk and lower legs often follow in succession.
- Once the eruption has started, cutaneous lesions will become more severe and widespread over the following several days to a week and will then clear over the next 7 to 14 days.
- Multiple drugs are associated with an exanthematous eruption including the penicillins, sulfonamides, barbiturates, and seizure medications.
- Amoxicillin-induced morbilliform eruptions are mediated by a T-cell immune reaction, which may explain the increased incidence of this eruption when a patient is infected with the Epstein-Barr virus (acute mononucleosis).³

B. Urticaria

- The second most common type of cutaneous drug eruption.
- Urticarial eruptions may be due to pseudoallergic, type I-, or type III-mediated reactions.
- Characterized by multiple pruritic wheals, widely scattered on the body. Individual lesions last <24 hours.
- Angioedema may accompany urticaria and may result in eyelid, lip, and mucous membrane swelling.
- The differential diagnosis of urticaria includes urticarial lesions due to vasculitis and/or serum sickness.
- Angiotensin-converting enzyme (ACE) inhibitors are frequent causes of angioedema, often without urticaria, with the reaction occurring within an hour or several months of its administration.

C. Serum Sickness–Like Reaction

- Serum sickness–like eruptions consist of fever, a rash with usually urticarial features, and arthralgias occurring within 1 to 3 weeks of initiation of the drug. Lymphadenopathy and eosinophilia may also be found.
- Two of the most common drugs to induce this reaction are cefaclor and minocycline.
- Treat with a short course of oral corticosteroids if symptoms are severe.

D. Acute Generalized Exanthematous Pustulosis

- Characterized by the sudden onset of fever, leukocytosis, and a generalized eruption of monomorphous sterile pustules on a background of edema and erythema.
- Discontinuation of the drug is usually all that is necessary.
- Desquamation will occur 2 weeks later.
- The most common offending drugs are the β -lactam and macrolide antibiotics (Table 12-1).

E. Fixed Drug Eruption

- Lesions develop 1 to 2 weeks after a first exposure; with subsequent exposures they may appear within 24 hours.
- Round and sharply demarcated erythematous plaques with possible central erosions are found anywhere on the body, but tend to favor lips, face, hands, feet, and genitalia.
- Lesions fade over several days, often leaving residual postinflammatory hyperpigmentation. A nonpigmented variant of FDE is of note as it is commonly caused after the administration of pseudoephedrine.

TABLE 12-1 Clinical Presentation and Selected Drug Etiology, Workup, and Treatment

Clinical Presentation	Description	Time Interval	Common Etiologic Drugs	Workup and Treatment
Exanthematous reactions	Morbilloform or maculopapular with rash beginning and ending on face and upper extremities, torso and lower extremities follow	7–14 d after initiation	Allopurinol, aminopenicillins, anticonvulsants, cephalosporins, and sulfonamides	
Urticaria ± angioedema	Multiple pruritic wheals, angioedema presents in lips, eyes, and mucous membranes	Onset is minutes to hours. Individual lesions last <24 h	Penicillins, cephalosporins, NSAIDs, monoclonal antibodies, contrast media, ACE inhibitors	Epinephrine
Anaphylaxis ^a				
Serum sickness–like reactions	Fever, urticarial rash, and arthralgias ± lymphadenopathy and eosinophilia	1–3 wk of initiation of the drug	Cefaclor, minocycline	Glucocorticosteroids (GCS) if severe
Acute generalized exanthematous pustulosis	Sudden onset of fever, leukocytosis, and a generalized eruption of monomorphic sterile pustules on a background of edema and erythema	<4 d	β-Lactam antibiotics, macrolides, calcium channel blockers	
Fixed drug eruption	Sharply demarcated erythematous and edematous plaques favoring lips, face, hands, feet, and genitalia, ± central blister	1–2 wk after a first exposure; with later exposures, they appear within 24 h. Last several days often leaving postinflammatory hyperpigmentation	Tetracyclines, barbiturates, sulfonamides, NSAIDs, salicylates	Characteristic histopathology. Patch testing in a previously involved site can be useful (avoid the refractory period)

Drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome	Exanthem, hepatitis (and other organ involvement), and fever	15–40 d	Anticonvulsants (aromatic), sulfonamides, allopurinol, lamotrigine, minocycline	Labs: CBC, liver function test, urinalysis, serum creatinine. Treat with systemic GCS
Drug-induced systemic lupus erythematosus	Weight loss, pericarditis, and pleuritic inflammation; cutaneous involvement is rare	Symptoms last 4–6 wk after withdrawal	Procainamide, hydralazine, chlorpromazine, isoniazid, methyldopa, propylthiouracil, quinidine, minocycline	Positive antihistone antibodies (nonspecific), negative double-stranded DNA
Drug-induced subacute cutaneous lupus erythematosus	Psoriasiform and annular lesions	Variable onset, resolution may not occur after withdrawal	Hydrochlorothiazide, calcium channel blockers, terbinafine, NSAIDs, griseofulvin	Anti-ro/SSA and anti-La/SSB antibodies
Erythema multiforme	Targetoid lesions, usually involving palms/soles	Lesions appear within 2 d and remain stable for 7 d	NSAIDs, sulfonamides, antiepileptics, antibiotics, others	For severe and debilitating mucosal involvement: short courses of oral GCS
SJS/TEN	Skin blisters and mucous erosions occur with extensive epidermal detachment and sloughing (<30%) BSA is SJS. >30% is TEN		Sulfonamides, anticonvulsants, allopurinol, NSAIDs, lamotrigine, Consider IVig	Transfer to a burn center. Symptomatic treatment only

ACE, angiotensin-converting enzyme; BSA, body surface area; CBC, complete blood count; GCS, glucocorticoids; NSAIDs, nonsteroidal anti-inflammatory drugs; SJS, Steven-Johnson syndrome; TEN, toxic epidermal necrolysis.

^aPresents as angioedema without wheals.

- Upon readministration of the causative drug, the lesions recur at the exact same locations, with potential to involve additional sites at each readministration.
- The presence of numerous lesions is referred to as generalized FDE, and it may be difficult to distinguish from EM or SJS (when the oral mucosa is also involved).
- Differential diagnosis includes spider or arthropod bite reaction, and EM or SJS when many lesions are present, particularly at mucous membranes.
- Common etiologic agents for FDE include sulfonamides, nonsteroidal anti-inflammatory drugs, barbiturates, tetracycline, and carbamazepine (Table 12-1).

F. Drug Reaction with Eosinophilia and Systemic Symptoms/Drug-Induced Hypersensitivity Syndrome

- A severe idiosyncratic reaction including an exanthem-type rash, facial edema, and fever, with associated systemic symptoms such as hepatitis, interstitial nephritis, arthralgias, lymphadenopathy, and hematologic abnormalities.
- Usually occurs within the first 1 to 6 weeks of the initial exposure to the drug, with a reaction rate of 1:3,000.
- Immunologic mechanisms play an important role as well as familial tendencies related to detoxification of drug metabolites. Cross-reaction occurs between the three aromatic anticonvulsants (phenytoin, carbamazepine, and phenobarbital) in 75% of patients. Lamotrigine does not cross-react with this group of drugs, but is also associated with cases of DRESS.
- Minocycline, allopurinol, sulfonamides, and dapsone have been associated with a similar syndrome. Erythromycin can cause elevated liver function tests, eosinophilia, and fever (Table 12-1).
- If a DRESS/DIHS is suspected, the clinician should obtain:
 - Serial liver function tests
 - Urinalysis
 - Serum creatinine
 - Complete blood count (CBC)
- If diagnosed:

A baseline thyroid-stimulating hormone (TSH) should be measured at the time of diagnosis and rechecked in 2 to 3 months. Hypothyroidism may develop in a subset of these patients, usually within 2 months of the incident.

G. Drug-Induced Systemic Lupus

- Associated with arthralgias, arthritis, fever, weight loss, pleuritis, and pericarditis. Skin findings are rare.
- A positive antinuclear antibody (ANA) is usually found in a subset of patients having antihistone antibodies but not antideoxyribonucleic acid antibodies.
- The drugs involved in this reaction include procainamide, hydralazine, isoniazid, penicillamine, methyldopa, and minocycline (Table 12-1).

H. Drug-Induced Subacute Cutaneous Lupus Erythematosus

- This is distinct from aforementioned drug-induced lupus and presents with photodistributed diffuse erythema and subacute cutaneous lupus erythematosus-type lesions *without systemic complaints*.
- ANA, anti-Ro/SSA, and anti-La/SSB antibodies may be present.

- Hydrochlorothiazide, calcium channel blockers, ACE inhibitors, statins, and terbinafine have been associated with drug-induced cutaneous lupus (Table 12-1).

I. Erythema Multiforme

- Characterized by distinctive target-shaped skin lesions. Lesions tend to affect the distal extremities, including the palms and soles.
- EM has diagnostic histology and is most often caused by infections (typically herpes simplex virus or *Mycoplasma pneumoniae*). Rarely caused by ADR.
- Lesions all appear within 2 days and remain stable for 7 days.

J. Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

- The exact mechanisms are not understood; however, cell-mediated cytotoxic reaction to epidermal cells may play a role.
- There is a genetic propensity for SJS and TEN, having a strong association between human leukocyte antigen markers.
- Symptoms are acute and begin within 4 weeks of drug exposure.
- Initial symptoms include a prodromal phase of fever, sore throat, and stinging eyes.
- The skin blisters and mucous erosions occur 1 to 2 days later, with extensive epidermal detachment and sloughing. Initially, the lesions are irregularly shaped, erythematous, purpuric macules that progressively coalesce. The mucous membranes are involved in the majority of cases.
- A marked loss of fluids, a drop in blood pressure, electrolyte disturbances, and infection may occur. SJS and TEN have a high mortality rate.
- Discontinuation of the causative agent is vital. Treatment is mainly symptomatic and supportive. Many also believe in the utility of IVIg in early TEN, however, this remains somewhat controversial.

Less common forms of drug reactions, which will not be discussed in detail, include erythema nodosum, leukocytoclastic vasculitis, bullous and pustular drug eruptions, lichen planus-like eruptions, abnormal pigmentary reactions, neutrophilic eccrine hidradenitis secondary to chemotherapeutic agents, pseudolymphoma, and exfoliative dermatitis. Additional drugs may exacerbate underlying dermatoses (e.g., β -blockers can worsen psoriasis and lithium can exacerbate acne).

III. WORKUP

A. Clinical Presentation. Mild-to-severe pruritus is the predominant symptom of urticarial and exanthematous drug eruptions. Inquire about symptoms of fevers, chills, malaise, arthralgias, myalgias, and dyspnea. Evaluate for extracutaneous signs such as fever, tachycardia, hypotension, lymphadenopathy, synovitis, and tachypnea. A complete skin examination should be performed including assessment of the palms, soles, and mucous membranes. Mild petechiae or frank nonpalpable purpura on the lower extremities is commonly associated with a vigorous eruption, but this does not imply that vasculitis or thrombocytopenia is present. More serious and violent reactions may include bullae, erosions, extensive purpura, or sloughing. Palpable purpuric lesions that do not blanch on pressure (diascopy) suggest vasculitis. Many types of drugs can produce identical eruptions; the morphology of the rash usually gives little clue as to the causative agent.

B. Other Differential Diagnoses. Consider viral exanthems, bacterial toxins, collagen vascular disease, primary skin conditions, and neoplasia.

C. Detailed Drug History. Questions about offending drugs must be detailed and direct, including:

- Prescription medications
- Eye/ear drops
- Nasal sprays
- Injections
- Over-the-counter medications (aspirin, suppositories, laxatives, sedatives), vitamins, and herbal supplements
- Immunizations
- Length of treatment
- Time frame of the reaction including onset and resolution
- Has the patient had similar episodes in the past?
- Does the patient have an underlying condition that would favor an adverse reaction to certain medications?
- For example, patients given ampicillin during the course of infectious mononucleosis have elevated rates of exanthematous type of reactions. Additionally, patients given sulfamethoxazole–trimethoprim while having acquired immunodeficiency syndrome experience higher rates of adverse reactions.

Specific questioning concerning nonmedical items such as preservatives, tonics, toothpaste, and topical lotions must also be considered. Penicillin is present in small amounts in some biologic products (such as poliomyelitis vaccine) and in dairy products from cows treated for mastitis. The possibility of illicit drugs must be considered. Tools such as the Naranjo ADR probability scale, while not commonly used in clinical practice, may be helpful in clarifying the probability that the adverse event is related to drug therapy.

In general, any new drug started within the past 2 to 3 months should be considered. Drug-induced lupus (e.g., minocycline) may not manifest until after a year or more of therapy. A review of the medical literature may provide information about the frequency of specific types of drug eruptions associated with a given drug. However, all drugs need to be considered a possible cause of any reaction.

Penicillin drugs, sulfonamides, and blood products are the most common causes of cutaneous reactions to drugs (Table 12-2). Amoxicillin, for instance, can be expected to incite an eruption in approximately 5% of courses of drug therapy. Drug-specific quantitative data are available to help evaluate which agents are most likely causes of drug-induced rash, itching, or hives. This information gives reaction rates for all commonly used drugs and allows one to calculate which drug might have caused an adverse reaction.⁴

D. Diagnostic Workup. Skin biopsies may help distinguish between a drug-induced condition and primary skin disease, e.g., differentiating between TEN and bullous pemphigoid. Blood workup may also aid in the clinical diagnosis. In a patient with systemic symptoms or signs, blood workup may be needed to determine the extent of internal organ involvement. A CBC with differential may show atypical lymphocytosis, leukopenia, leukocytosis, and eosinophilia. Liver function tests, serum creatinine, urinalysis, and TSH may be indicated in patients with suspected DIHS. Abnormal blood tests should be repeated during the convalescent period and TSH rechecked

TABLE 12-2 **Drugs with Reaction Rates <1%**

Drug	Reaction Rate (Reactions/1,000 Recipients)
Amoxicillin	51
Trimethoprim–sulfamethoxazole	34
Ampicillin	33
Blood	22
Cephalosporins	21
Semisynthetic penicillin	21
Erythromycin	20
Penicillin G	19
Cyanocobalamin	18
Quinidine	13
Cimetidine	13
Phenylbutazone	12

(Data from Bigby M, Jick S, Jick H, et al. Drug-induced cutaneous reactions: a report from the Boston Collaborative Surveillance Program on 15,438 consecutive inpatients, 1975 to 1982. *JAMA*. 1986;256:3358-3363.)

in 3 months. Cultures of skin, blood, tissue, erythrocyte sedimentation rate, ANA, and other tests may be ordered to help confirm or rule out other conditions. If palpable purpuric lesions are present, a complete physical and laboratory examination is required with an eye toward ruling out vasculitic involvement of other organ systems and other causes of vasculitis such as infection and collagen vascular disease. A skin biopsy should be considered to confirm the diagnosis.

Apart from clinical challenge, there is no consistently reliable test to confirm that a drug is the cause of an adverse reaction. Given the laboriousness and the medical risks, oral provocation tests are rarely performed; they are never performed on patients who have had severe reactions. A topical rechallenge with the suspected drug may be helpful in patients with fixed drug eruptions. Skin testing with haptenized penicillin (penicilloyl–polylysine) can accurately predict reactions to penicillins. Skin prick testing with major and minor determinants is useful for confirmation of an IgE-mediated allergic reaction to penicillin.⁵ Radioallergosorbent test on serum for penicillin allergy will give similar data without the danger of injecting an allergenic drug.

The use of patch testing for cutaneous drug eruptions is not standardized, and its diagnostic value in this situation is unproven. Patch testing may be particularly helpful in patients with a systemic contact-type drug eruption, originally sensitized by topical application, and in AGEP, where the offending agent may illicit an isomorphic pustular reaction. Patch testing may occasionally be

helpful in fixed drug eruptions. The frequency of positive patch test reactions in patients with a history of a drug exanthema to any medication is approximately 10% to 11%. In patients with a history of an exanthematous drug eruption to antibiotics, 31% to 83% may have positive patch test reactions.⁶

IV. TREATMENT

1. Discontinue the offending drug.
2. Administer oral antihistamines.
3. Soothing tepid water baths with cornstarch and/or cool compresses may be useful.
4. An antipruritic lotion (containing camphor and/or menthol) or lubricating antipruritic emollients applied p.r.n. will help relieve the pruritus.
5. Topical steroids may provide some relief.
6. If signs and symptoms are severe, a 2-week course of systemic corticosteroids (prednisone, starting at 60 mg) or injection of a repository corticosteroid preparation will usually stop the symptoms and prevent further progression of the eruption within 48 hours of the onset of therapy.
7. Sulfamethoxazole–trimethoprim desensitization with a strict protocol and close observation can be undertaken in patients with human immunodeficiency virus who have a high cutaneous reaction rate to this drug.
8. Cephalosporins rarely cross-react in a penicillin-allergic patient. The overall incidence of allergic reactions to cephalosporins is low and usually mild (rash, urticaria). The incidence of drug reactions in penicillin-allergic patients was 0.04%.⁷
9. Review warnings about cross-reacting drugs and risk of family members for patients who have had severe reactions such as DRESS/DIHS and SJS/TEN (Table 12-3).

TABLE 12-3		Medication Classes Implicated with Cutaneous Adverse Drug Reactions	
Medication Class	Est. Number of Cases (1995–2005)	% of All Cases	
Antibiotics	1,602,508	22.9	
Penicillins	388,291	5.6	
Sulfonamides	203,326 ^a	2.9	
Cardiovascular agents	494,732 ^a	7.1	
Agents primarily affecting skin and mucous membrane	422,758 ^a	6.0	
Hormones and synthetic substitutes	413,261 ^a	5.9	
Adrenal cortical steroids	339,430 ^a	4.9	

TABLE 12-3 (Continued)

Analgesics, antipyretics, and antirheumatics	170,531 ^a	2.4
Antiallergics/antiemetics	119,480 ^a	1.7
Vaccines	118,192 ^a	1.7
CNS agents	83,172 ^a	1.2
Other specified drugs	1,205,489	17.2
Unspecified/unknown	1,722,745	24.6
No cause stated	1,266,002	18.1

^aEstimates based on less than 30 visit records.

(Koelblinger P, Gustafson C, Debadé T, Davis S, Feldman S. *Skin Manifestations of Outpatient Adverse Drug Events in the United States: A National Analysis*. Presentation presented at 70th Annual Meeting of the American Academy of Dermatology, 2012 March 16–20; San Diego, CA.)

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REFERENCES

1. Koelblinger P, Gustafson C, Debadé T, Davis S, Feldman S. *Skin Manifestations of Outpatient Adverse Drug Events in the United States: A National Analysis*. Presentation Presented at 70th Annual Meeting of the American Academy of Dermatology, 2012 March 16–20; San Diego, CA.
2. Lazarou J, Pomeranz BH, Carey PN. Incidence of adverse drug reactions in hospitalized patients. A meta-analysis of prospective studies. *JAMA*. 1998;279:1200-1205.
3. Barboud AM, Bene MC, Schmutz JL, et al. Role of delayed cellular hypersensitivity and adhesion molecules in amoxicillin-induced morbilliform rashes. *Arch Dermatol*. 1997;133:481-486.
4. Bigby M. Rates of cutaneous reactions to drugs. *Arch Dermatol*. 2001;137(6):765-770.
5. Sogn D, Evans R III, Shephard GM, et al. Results of the National Institute of Allergy and Infectious Diseases Collaborative Clinical Trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. *Arch Intern Med*. 1992;152:1025.
6. Cham P, Warshaw EM. Patch testing for evaluating drug reactions due to systemic antibiotics. *Dermatitis*. 2007;18(2):63-77.
7. Ann S, Reisman RE. Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. *Ann Allergy Asthma Immunol*. 1995;74:167-170.

Suggested Reading

Khan D, Solensky R: Drug allergy. *J Allergy Clin Immunol*. 2010;125:S126-S137.

I. BACKGROUND Xerosis (dry skin, asteatosis) is one of the most common dermatologic conditions, characterized clinically by dry, rough, and scaly skin. It is frequently found in the elderly population and in those living in dry climates. Xerosis more commonly involves the lower legs; however, any site may be affected. Asteatotic eczema, a condition frequently found in the elderly during the wintertime, is a superimposed dermatitis on xerosis. Dry skin can result from both endogenous and exogenous causes. Endogenous causes include malnutrition leading to hypovitaminosis, renal disease, underlying malignancies (especially Hodgkin lymphoma), human immunodeficiency virus, hypothyroidism, and hereditary diseases such as ichthyosis vulgaris and atopic dermatitis. Exogenous causes include cold, dry, windy climates, low indoor humidity, excessive exposure to water, soaps and surfactants, and drugs (i.e., lithium, diuretics, and isotretinoin). The pathogenesis of xerosis may be attributed to a decrease in stratum corneum lipids, resulting in impaired barrier function and decreased synthesis of the “natural moisturizing factor.” This results in reduced water-binding capacity of the stratum corneum leading to dehydration of the stratum corneum and the formation of dull, rough scales. This sequence of events may be a result of exposure to exogenous factors or represent dysfunction of the stratum corneum as a consequence of aging.

Ichthyosis vulgaris is an autosomal dominant disorder of keratinization with a prevalence of 1 in 250 individuals. It results from a loss of function mutation in the filaggrin gene. Filaggrin deficiency results in impaired squamous cell formation and transepidermal water loss. Clinical manifestations are not present at birth, typically appearing early childhood. The clinical findings in ichthyosis vulgaris overlap with xerosis and often cannot be differentiated (Table 13-1). Ichthyosis vulgaris is frequently associated with the atopic triad of asthma, allergic rhinitis, and atopic dermatitis. Laboratory workup may reveal endogenous or exogenous causes of dry skin discussed previously (Table 13-2).

II. CLINICAL PRESENTATION Mild xerosis is usually asymptomatic, but severe xerosis is often associated with pruritus and a stinging sensation. Xerosis initially starts on the lower legs, then spreads to involve the proximal extremities and trunk, often sparing the face, neck, palms, and soles. The skin appears dry and dull, with bran-like scales. With more severe involvement, the skin exhibits superficial cracks and fissures in a pattern that has been likened to a “dried riverbed.” With asteatotic eczema, there is underlying erythema often with excoriations, crusting, and nummular plaques present.

Ichthyosis vulgaris is characterized by fine, white, flaky scale especially on the extensor surfaces of the extremities (Fig. 13-1). The scales on the lower legs

TABLE 13-1 **Differential Diagnosis****Dry Skin:**

- Ichthyosis vulgaris
- Asteatotic dermatitis
- Atopic dermatitis
- Malnutrition
- Hypothyroidism

Ichthyosis Vulgaris:

- Xerosis
- Atopic dermatitis
- X-linked ichthyosis
- Steroid sulfatase deficiency
- Occult malignancy

TABLE 13-2 **Laboratory Workup**

- Complete blood count
- Blood urea nitrogen
- Creatinine
- Thyroid-stimulating hormone
- Human immunodeficiency virus

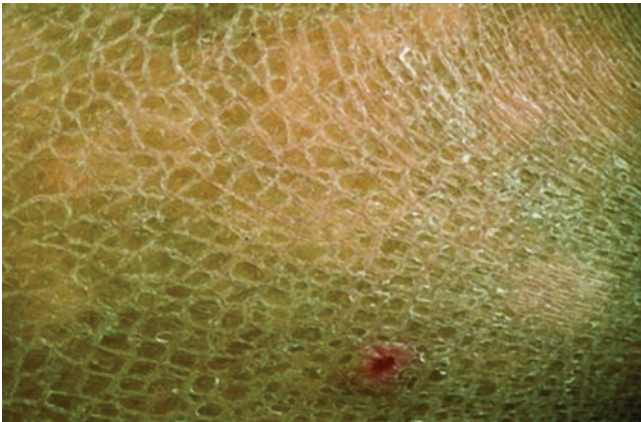


Figure 13-1. Ichthyosis vulgaris. (From Elder AD, Elenitsas R, Johnson BL, et al. *Synopsis and Atlas of Lever's Histopathology of the Skin*. Philadelphia, PA: Lippincott Williams & Wilkins; 1999, p. 2, clin. fig. IA1; p. 163, clin. fig. IVE3; p. 167.)

tend to be larger with an adherent center and detached outward edges. Flexural areas are spared secondary to increased humidity in these areas. Keratosis pilaris (follicular accentuation and keratinization) may be prominent over the arms, thighs, and buttocks. The palms and soles may have mild hyperkeratosis leading to accentuated skin lines.

III. WORKUP It is important to obtain a detailed family history, medication history, history of occupational exposures, and hobbies that may provide clues to causative or exacerbating factors. A comprehensive review of systems may also be helpful in excluding underlying systemic diseases as previously discussed.

IV. TREATMENT Dry skin in affected individuals is primarily due to the lack of water as opposed to lack of oils (sebum production) in the skin. Therefore, all therapeutic treatments are aimed at increasing hydration of the skin by either preventing water loss or by effectively replenishing water in the skin (Table 13-3).

A. Preventative Measures

1. Keep room temperatures cool.
2. Recommend the use of vaporizers and cool-air humidifiers in dry rooms.
3. If bathing daily, use warm water, not hot, for 10 minutes or less with nonsoap cleansers only around the axillae/groin area and hands/feet. Avoid bubble baths and the use of body washes.¹
4. After bathing, emollients should be applied within 3 minutes while the skin is still moist in order to trap the moisture. Emollients include mineral oils, waxes, fatty acids, and triglycerides.¹ Apply moisturizers or emollients liberally at least once daily.
5. Rough clothing (such as wool) should be avoided to reduce irritation to the skin. Instead choose cotton or linen clothing that is loose to allow for good circulation. Recently, it has been shown that the use of fabric softeners can improve the stratum corneum water content; therefore, it can be used as a protective measure against dry skin.²
6. Limit sun exposure.
7. If able, relocate during the winter season to a subtropical environment.

B. Treatment of Xerosis/Ichthyosis Vulgaris

1. The most effective way to relieve dry skin is through the application of water on the skin followed by a hydrophobic substance (moisturizer) to prevent water from leaving. This is done by soaking the affected area

TABLE 13-3	Primary Treatment Options
1.	Lifestyle modifications to eliminate factors that aggravate dry skin
2.	Topical emollients (especially those containing humectants and ceramides)
3.	Keratolytics
4.	Mild topical corticosteroids for asteatotic dermatitis

and then immediately applying a water-in-oil or fatty hydrophobic medication to achieve maximal hydration of the stratum corneum. This is why it is imperative to apply moisturizers after bathing, because moisturizers do not put water back into the skin externally, they must work by attempting to halt transepidermal water loss. Moisturization of the skin also helps to create an optimal environment for restoration of the stratum corneum.

2. Humectant agents are more potent due to their ability to attract moisture from the air and hold water in the skin, thereby rehydrating the stratum corneum.¹ Such agents include lactic acid, glycolic acid, urea, glycerin, propylene glycol, sorbitol, carboxylic acid, gelatin, and hyaluronic acid. They are helpful when emollients fail to achieve significant improvement.
3. If dry skin persists after treatment with either emollients or moisturizers, lamellar-forming ingredients such as ceramides, pseudoceramides, and phospholipids have recently been shown to surpass a mineral oil-containing substance (like emollients) in the relief of dry skin. A novel complex of lipophilic ingredients such as cetyl alcohol, isostearyl isostearate, potassium cetyl phosphate, cetyl behenate, and behenic acid was shown to significantly improve dry skin.³ Because ceramides account for approximately 50% of the total stratum corneum lipid mass, ceramide-containing moisturizers incorporate into the lamellar envelope, thus restoring the stratum corneum barrier.
4. For patients with ichthyosis vulgaris, topical 10% urea-based lotion was shown to improve symptoms in comparison to glycerol-based emollient creams.⁴ Urea creams or lotions promote desquamation leading to a decreased transepidermal water loss. In addition, a cream with urea and salicylic acid or lactic acid can be used for severe dry skin with fissures.¹ In extreme cases where dark scales are present, 40% to 60% propylene glycol plus 6% salicylic acid in water applied under plastic occlusion overnight can be used to remove the dark scales.
5. In more severe cases of xerosis, 40% to 60% propylene glycol in water bandaged with plastic overnight can also be used for maximum hydration.
6. Products that contain pramoxine–menthol or camphor are suggested for mild-to-moderate itchy dry skin.
7. In cases of severe itch, an oral antihistamine is recommended rather than topical antihistamines because the latter can cause contact sensitization.
8. If there is inflammation, then topical steroids or calcineurin inhibitors may be used.¹

REFERENCES

1. Guenther L, Lynde CW, Andriessen A, et al. Pathway to dry skin prevention and treatment. *J Cutan Med Surg.* 2012;16:23-31.
2. Isoda K, Takagi Y, Kitahara T, et al. Treatment of cloth with a fabric softener ameliorates skin dryness. *J Dermatol.* 2011;38:685-692.
3. Pennick G, Chavan B, Summers B, et al. The effect of an amphiphilic self-assembled lipid lamellar phase on the relief of dry skin. *Int J Cosmet Sci.* 2012;34:567-574.

4. Tadini G, Giustini S, Milani M. Efficacy of topical 10% urea-based lotion in patients with ichthyosis vulgaris: a two-center, randomized, controlled, single-blind, right-vs.-left study in comparison with standard glycerol-based emollient cream. *Curr Med Res Opin.* 2011;27:2279-2284.

Suggested Readings

- Harding CR. The stratum corneum: structure and function in health and disease. *Dermatol Ther.* 2004;17:6-15.
- White-Chu EF, Reddy M. Dry skin in the elderly: complexities of a common problem. *Clin Dermatol.* 2011;29(1):37-42.

ERYTHEMA MULTIFORME

I. BACKGROUND Erythema multiforme (EM) is an acute, immune-mediated disorder. Ninety percent of EM cases are attributable to infection, the most common being herpes simplex virus (HSV). Clinical findings in HSV-associated EM are thought to be secondary to an immune-mediated response against viral antigen-positive cells containing HSV DNA polymerase *pol*. Additional etiologic factors implicated in the development of EM, including medications and other infections, are listed in Table 14-1. Medications are believed to incite less than 10% of EM cases.

II. CLINICAL PRESENTATION EM presents with isolated cutaneous lesions, isolated mucosal lesions, or a combination of the two. Previously, EM was considered to represent a spectrum of disease, including EM minor and major, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). Now, however, EM major and SJS are considered distinct clinical entities with similar mucosal erosions, but differing cutaneous lesions.

Prodromal symptoms, including fever, malaise, and myalgias, may be present, most commonly when there is mucosal involvement. The classic lesions of EM are targetoid in appearance and comprise the following features: a central area of dusky epidermal necrosis, a concentric dark red inflammatory ring surrounded by a lighter, edematous ring with an outer zone of erythema. The lesions may change in morphology over the course of the episode, and geographic, polycyclic, and annular configurations have been described. In addition, some lesions may appear “atypical” in that they consist of ill-defined, two-zoned targets. Figure 14-1 depicts typical targetoid lesions.

Mucosal lesions occur in 25% to 60% of EM episodes (Fig. 14-2). The oral mucosa is most commonly involved. Lesions present with erythema and

TABLE 14-1 Most Common Causes of Isolated Erythema Multiforme

Causes

Infections	Herpes simplex virus <i>Mycoplasma pneumoniae</i>
Drugs	Nonsteroidal anti-inflammatory drugs Sulfonamides Antiepileptics Other antibiotics



Figure 14-1. This patient has a recurrent HSV infection. Note the drying crust of the herpetic lesion on his lower lip and the target-like lesions on his palm. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 14-2. Mucosal erosions on the lip. (From Fleisher GR, Ludwig S, Baskin MN. *Atlas of Pediatric Emergency Medicine*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

edema and progress to superficial erosions. Symptoms of burning, swelling, and pain can lead to poor oral intake. Importantly, involvement of the ocular and upper respiratory mucosa may occur. Sequelae from mucosal involvement include keratitis, conjunctival scarring, uveitis, permanent visual impairment, esophagitis with strictures, and upper airway erosions leading to pneumonia.

Classic EM is an isolated, self-limiting disease. The time from disease onset to resolution is usually less than 4 weeks, but can take up to 6 weeks if mucous

membranes are involved. A subset of EM cases are recurrent (\geq six episodes per year) and are mostly triggered by recurrent HSV infection. Other cases of EM can be persistent, in that lesions are continuous and uninterrupted.

III. WORKUP No laboratory markers or histopathologic evaluation are required for the diagnosis of EM. Clinical history is paramount in rendering the diagnosis. It is important to inquire about signs and symptoms of infection (HSV or *Mycoplasma pneumoniae*) and to review the use of new medications. The timing of symptoms is also relevant in determining if the patient has an isolated, episodic, or persistent case of EM.

While it is not necessary for diagnostic confirmation, a skin biopsy may be helpful to exclude other conditions. If HSV lesions are suspected on physical examination, viral culture, HSV polymerase chain reaction (PCR), and/or direct fluorescent antibody should be obtained. When respiratory symptoms are present, *M. pneumoniae* serologic testing, chest radiograph, and/or throat swab PCR for *M. pneumoniae* can be obtained. Recurrent idiopathic EM or persistent EM may be further investigated with serologic HSV testing, molecular in situ hybridization/PCR of tissue for HSV, and selected laboratory tests to rule out underlying infectious, inflammatory, autoimmune, or malignant disorders.

Although exceedingly rare, there have been reports linking EM with underlying leukemias and lymphomas. In patients with persistent, recalcitrant EM, solid organ cancers have been described, including gastric adenocarcinoma, renal cell carcinoma, and extrahepatic cholangiocarcinoma.

IV. TREATMENT (Table 14-2)

A. Acute Cutaneous Erythema Multiforme

- Possible inciting medications should be discontinued.
- Topical corticosteroids and oral antihistamines can be used for symptomatic relief of itching and burning of cutaneous lesions.
- For suspected HSV-induced EM, antiviral therapy may be considered, but is controversial. Typically, HSV infection precedes EM cutaneous lesions by approximately 8 days. Studies have shown that administration of antiviral medications for the treatment of active postherpetic EM does not alter the clinical course.

B. Mucosal Erythema Multiforme

- In minor cases, high potency topical corticosteroid gels, oral antiseptic wash, and oral anesthetic solutions are usually sufficient.
- When there is severe, painful mucosal involvement interfering with oral intake, oral corticosteroids may be used to decrease severity and duration of the symptoms. No controlled studies, however, support the usage of oral corticosteroids in the treatment of mucosal EM.

C. Recurrent Erythema Multiforme

- First-line treatment for HSV-associated recurrent EM or idiopathic recurrent EM is a 6-month trial of antiviral therapy.
- The following antivirals have been used: acyclovir, valacyclovir, and famciclovir.
- For unresponsive cases, the dose can be doubled or the therapy switched to an alternative antiviral.

- Other treatments that have been used for recurrent EM, but have not been validated in controlled trials, include the following: dapsone, mycophenolate mofetil, azathioprine, hydroxychloroquine, cimetidine, immunoglobulin, thalidomide, and cyclosporine.

STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

I. BACKGROUND SJS and TEN are uncommon, acute drug reactions. The incidence is estimated to be 1.5 to 2 new cases per million people per year. Mortality of SJS/TEN ranges from 10% to 40%. Apoptosis of keratinocytes is believed to be the mechanism responsible for keratinocyte death in SJS/TEN. One theory proposes that an inciting drug activates cytotoxic T cells, leading to the release of granzyme B and perforin, thus activating a caspase cascade resulting in keratinocyte apoptosis. A second theory proposes that Fas–Fas ligand binding activates caspase 8, which results in nuclease activation and severe skin blistering.

II. CLINICAL PRESENTATION The presentation of cutaneous lesions is often preceded by a prodromal phase consisting of symptoms that mimic an upper respiratory tract infection; patients may experience fever, sore throat, cough, vomiting, diarrhea, lethargy, and myalgia.

The primary cutaneous lesions of SJS/TEN can be erythematous to dusky macules, flat atypical targets, bullae, erosions, or necrosis. Atypical targets consist of two-ring lesions with a dark red center, and a lighter red halo or red macules with central blistering. Lesions are painful and exhibit Nikolsky sign (epidermal separation induced by lateral pressure). Epidermal sheet-like detachment may occur (Figs. 14-3 and 14-4). SJS and TEN are defined by the percentage of body surface area (BSA) of epidermal attachment: SJS <10%, SJS/TEN overlap 10% to 30%, and TEN >30%. Mucosal involvement is common and usually involves two or more sites. Ocular, oropharyngeal, respiratory, gastrointestinal, and genital mucosa may be affected. In addition to oral erosions and blisters, patients may have hypoxemia from sloughing of bronchial epithelium, purulent conjunctivitis and pseudomembrane formation, rectal bleeding, or dysuria and hematuria from genitourinary mucosal involvement.

TABLE 14-2 Treatment Based on the Type of Erythema Multiforme		
Isolated Cutaneous	Mucosal	Recurrent
1. Topical corticosteroids and antihistamines	1. Mild <ul style="list-style-type: none">• Topical corticosteroids• Antiseptic wash• Anesthetic wash	First-line therapy 6-mo continuous treatment with acyclovir, valacyclovir, or famciclovir
2. Discontinuation of medication (if implicated)	2. Severe involvement Consider oral corticosteroid course tapered over 2–4 wk	
3. Consider treatment of herpes simplex virus or <i>Mycoplasma pneumoniae</i> infections		



Figure 14-3. Epidermal detachment seen in SJS/TEN. (Courtesy of Julia Kasprzak, MD.)



Figure 14-4. Blisters and erosions seen in SJS/TEN. (Courtesy of Julia Kasprzak, MD.)

Septicemia from *Staphylococcus aureus* or *Pseudomonas aeruginosa* is the most frequent cause of death in patients with SJS/TEN. If patients survive the acute period, they may suffer from complications and long-term sequelae. Cutaneous scarring, dyschromia, and nail dystrophy may occur. Ocular lesions can result in entropion, symblepharon, synechiae, and blindness.

III. WORKUP Biopsy with frozen section may be performed early in the course of the disease to help exclude other diagnoses. Biopsy classically shows full-thickness epidermal necrosis, with a paucicellular lymphocytic infiltrate.

The causative medication/drug should be determined and stopped immediately. More than 220 medications have been implicated in triggering SJS/TEN; the most common of these are listed in Table 14-3. Genetically susceptible individuals with certain human leukocyte antigen (HLA) types have an increased risk of developing adverse drug reactions to certain medications. For example, patients with HLA-B1502 are at higher risk for the development of SJS/TEN when given carbamazepine. Also, patients with HLA-B5701 are prone to a hypersensitivity reaction to abacavir. A urine and serum toxicology screen should be considered if illicit substances are suspected.

The skin detachment in SJS/TEN causes water loss, electrolyte imbalances, and protein loss. Vital signs, electrolyte values, albumin levels, and complete blood counts should be monitored throughout the patient’s hospitalization. At the time of admission, the severity-of-illness score for TEN (SCORTEN) should be calculated (Table 14-4). This score calculates the probability of death from SJS/TEN based on seven independent risk factors.

TABLE 14-3 Common Drugs Implicated in Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis	
Antibiotics	Sulfonamides, β -lactams, tetracyclines, and quinolones
Anticonvulsants	Phenytoin, phenobarbital, and carbamazepine (HLA-B1502), lamotrigine
Antivirals	Nevirapine and abacavir (HLA-B5701)
Other	Nonsteroidal anti-inflammatory drugs (particularly oxicams) Allopurinol

TABLE 14-4 SCORTEN—Independent Prognosis Factors and Mortality in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis		
Prognosis Factor		Score
Age	≥ 40 y	1
Malignancy	Yes	1
Body surface area	$\geq 10\%$	1
Heart rate	$\geq 120/\text{min}$	1
Serum urea	> 27 mg/dL	1
Serum glucose	> 250 mg/dL	1
Serum bicarbonate	> 20 mEq/L	1

TABLE 14-4 *(Continued)*

SCORTEN	Mortality Rate (%)
0–1	3.2
2	12.2
3	35.3
4	58.3
≥5	90

It is also important to perform a full physical examination at regular intervals during the patient's admission to evaluate for progression of percent BSA and mucosal involvement. Appropriate specialties (ophthalmology, gastroenterology, gynecology, genitourinary, and pulmonary) should be involved as necessary to monitor and avoid sequelae related to mucosal involvement.

IV. TREATMENT

A. General Care Patients should be admitted to a burn unit for continuous monitoring, isolation, and appropriate wound management. As mentioned above, it is most important to first stop the offending medication. Aggressive fluid and electrolyte replacement, serum protein and blood glucose control, and topical skin management are required. Nutritional replacement with total parenteral nutrition should be considered in patients who are unable to eat or drink due to oral involvement. Nutritional requirements appear to be related to the total percent BSA affected.

Antibiotics are warranted only if a positive culture is obtained; there is no evidence for the use of prophylactic antibiotics in SJS/TEN. Appropriate analgesia, and prophylaxis for gastric ulcers and deep venous thrombosis, should be approached in the same manner as in any critically ill patient. Daily physical therapy sessions can play an important role to preserve limb motility during hospitalization.

B. Wound Care Topical wound management is an essential part of the treatment of patients with SJS/TEN. Some authors are proponents of aggressive debridement, while others take a more conservative approach. It is important for the wound dressing to not only protect the exposed dermis but also maintain the physiologic conditions required for re-epithelialization and provide little to no restriction of movement. Silver sulfadiazine cream is commonly used to avoid infection; however, it cannot be used in those who have a history of hypersensitivity to sulfonamides and it requires frequent, painful wound dressings.

Other dressing options include biologic materials (cadaveric allografts, xenografts, and cultures of human allogenic or autologous epidermal sheets) or synthetic skin substitutes consisting of a synthetic bilaminar membrane. Nanocrystalline silver dressings are a more recent advancement in wound care for SJS/TEN, which combine antimicrobial and anti-inflammatory properties.

C. Pharmacologic Management Withdrawal of the suspected drug is the only measure that has been validated to reduce mortality in patients

with SJS/TEN. There is insufficient evidence to support the benefit for any other treatment. Various agents that take action on the immune system have been used in the treatment of SJS/TEN.

1. **Corticosteroids** For years, corticosteroids were the treatment of choice for patients with SJS/TEN. However, conflicting data exist on their use. Some studies report good results; some describe worsening of disease and increased mortality, and others report no change in mortality. Currently, corticosteroid use has fallen out of favor as a treatment due to increased risk of infection.
2. **Intravenous Immunoglobulin** Intravenous immunoglobulin (IVIG) blocks the cell surface Fas ligand that induces keratinocyte apoptosis. It is produced from donated blood plasma, which is fractionated and purified until obtaining a product that contains predominantly IgG and traces of IgA, IgM, CD4, CD8, HLA molecules, and cytokines. Before administration of IVIG, patient IgA levels must be measured. Those who are IgA deficient have a higher risk of severe systemic reactions, including anaphylactic shock, when receiving treatment. As with other treatments for SJS/TEN, there is a lack of randomized, controlled comparative trials involving IVIG. It has shown to be effective in limited cases. While the ideal dosing is unclear, some authors advocate dosages of 3 g/kg over a period of 3 days.
3. **Cyclosporine** This is a powerful immunosuppressant with specific action against T-lymphocyte activation and proliferation; it also blocks apoptotic reaction sequence. Isolated case reports have shown positive outcomes with the use of cyclosporine.
4. **Antitumor Necrosis Factor- α Agents** The theory of tumor necrosis factor (TNF) involvement in the pathophysiology of SJS/TEN has led to their use in some cases. An isolated case report showed improvement with the use of infliximab. However, another trial comparing thalidomide, which lowers the release of TNF- α from monocytes, with placebo showed increased mortality in the treated group. More studies are needed to determine the possible role of TNF- α inhibitors in the treatment of SJS/TEN.
5. **Plasmapheresis** This treatment is used to improve antibody-mediated disease and disease associated with immune complex formation. The whole blood volume is removed from the patient, which is then separated into plasma and cellular portions. The cellular portion is then reinfused with new plasma or albumin. Plasmapheresis has been reported in some publications to benefit SJS/TEN cases, but there has also been a series of patients that failed to respond.

Suggested Readings

- Assier H, Bastuji-Garin S, Revuz J, Roujeau JC. Erythema multiforme with mucous membrane involvement and Stevens–Johnson syndrome are clinically different disorders with distinct causes. *Arch Dermatol*. 1995;131:539-543.
- Bastuji-Garin, S, Fouchard N, Bertocchi M, et al. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol*. 2000;15(2):149-153.

- Lissia M, Mulas P, Bulla, A, Rubino C. Toxic epidermal necrolysis (Lyell's disease). *Burns*. 2010;36:152-156.
- Schneck J, Fagot, J, Sekula P, Sassolas B, Roujeau JC, Mockenhaupt M. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR study. *JAAD*. 2008;58:33-40.
- Sokumbi O, Wetter DA. Clinical features, diagnosis and treatment of erythema multiforme: a review for the practicing dermatologist. *Int J Dermatol*. 2012;51:889-902.
- Tatnall, FM, Schofield JK, Leigh IM. A double-blind, placebo-controlled trial of continuous acyclovir therapy in recurrent erythema multiforme. *Br J Dermatol*. 1995;132:267-270.

I. BACKGROUND Erythema nodosum (EN), the most common type of panniculitis (fat inflammation), is a reactive inflammatory condition. It occurs in association with a broad range of predisposing factors and disease processes and is most commonly attributed to an immune complex-mediated or type IV delayed hypersensitivity response to an inciting antigen. Various infections, drugs, systemic disease states, and malignancies have been associated with EN (Table 15-1). The relative frequency of etiologic agents varies by geographic location. Approximately 50% of cases are thought to be idiopathic. Pathologically, neutrophilic infiltration leads to the release of reactive oxygen species and oxidative tissue damage.

Upper respiratory tract infection secondary to β -hemolytic strep (*Streptococcus pyogenes*, Lancefield Group A) is the most common infectious cause of EN and the most frequent etiology in children. Other common etiologies include coccidioidomycosis and gastroenteritis secondary to *Yersinia*, *Salmonella*, or *Campylobacter* infections. Additional infectious causes such as tuberculosis must be considered in patients from endemic areas or with other risk factors.

Pharmaceutical agents that are commonly reported as causes of EN include estrogen-containing medications (e.g., oral contraceptives), sulfonamides, penicillin, and halogens (bromides and iodides). The incidence of oral contraceptive-associated EN has decreased with reduction in the hormone levels in these products. The high hormonal state of pregnancy can also trigger EN.

Sarcoidosis is the most common underlying inflammatory disease state associated with EN. Other less frequent etiologies include inflammatory bowel disease (Crohn disease > ulcerative colitis), Behçet's disease, and Sweet syndrome. Various malignancies have also been associated (Table 15-1).

II. CLINICAL PRESENTATION EN most commonly presents with a rapid onset of bilateral, erythematous, warm, tender nodules, and plaques on the pretibial lower legs (Fig. 15-1). Less common sites of involvement include the thighs and extensor forearms. Rarely, lesions on the head, neck, or trunk may be seen. These cutaneous findings are often preceded by a prodrome of fever, malaise, arthritis, and arthralgias (1 to 3 weeks prior to eruption). Associated cough, headache, gastrointestinal upset, ocular findings (conjunctivitis and episcleral lesions), lymphadenopathy, hepatosplenomegaly, and pleuritis have also been reported. While disease onset can occur at any age, EN most often presents between the second and fourth decades of life. There is a strong female predisposition, with a reported female to male ratio as high as 6:1 among adults.

Individual lesions of EN persist for approximately 2 weeks, followed by slow resolution without scarring. Although ulceration is extremely rare, subcutaneous

TABLE 15-1 **Reported Causes of Erythema Nodosum^a**

Infectious Agents (Bacterial)	Infectious Agents (Other)	Underlying Disease or Condition	Malignancies	Medications
<i>Streptococcus pyogenes</i> (Group A)	Epstein-Barr virus	Sarcoidosis	Acute myelogenous leukemia	Oral contraceptives (estrogen-containing products)
<i>Coccidioides immitis</i>	Hepatitis B and C	Crohn disease	Hodgkin disease	Penicillins
<i>Histoplasma capsulatum</i>	Herpes simplex virus	Ulcerative colitis	Pancreatic carcinoma	Sulfonamides
<i>Blastomyces dermatitidis</i>	Human immunodeficiency virus	Behçet's disease	Carcinoid tumor	Bromides
<i>Paracoccidioides brasiliensis</i>	Spirochetes (e.g., syphilis)	Sweet syndrome		Iodides
<i>Campylobacter</i>	Parasites	Pregnancy		
<i>Salmonella</i>				
<i>Yersinia</i>				
<i>Mycobacterium tuberculosis</i>				
<i>Mycoplasma pneumoniae</i>				
<i>Chlamydia pneumoniae</i>				
<i>Chlamydia trachomatis</i>				
<i>Brucella melitensis</i>				
<i>Bartonella</i> spp.				
<i>Rickettsiae</i>				

^aNot an exhaustive list.



Figure 15-1. Characteristic erythematous nodules of erythema nodosum.

hemorrhage often does occur, leading to a bruise-like appearance (erythema contusiformis) in late-stage lesions. Additional new crops of lesions may erupt for as long as 6 weeks after the initial presentation. Rare, chronic variants of EN have also been described (EN migrans and subacute nodular migratory panniculitis). Arthralgias and rheumatoid factor–negative arthritis have been reported to persist in the absence of recurrent EN lesions.

Lofgren syndrome is the finding of EN in association with the acute phase of sarcoidosis. In caucasian patients, this association often signals a more benign course of sarcoidosis. Lofgren is commonly accompanied by polyarthralgias, most often of the ankles and knees. Radiologic evaluation of the chest often reveals bilateral hilar lymphadenopathy (stage I sarcoidosis). Of note, this lymphadenopathy tends to be relatively symmetric, with slight right-sided predominance. In most cases of perihilar lymphadenopathy secondary to tuberculosis or malignancy, the lymph node involvement tends to be more asymmetric.

III. WORKUP A full history and examination should be obtained in any patient presenting with EN lesions. The patient should be questioned about any preceding throat symptoms, which may suggest an inciting streptococcal infection. Throat cultures, polymerase chain reaction assays, and/or anti-streptolysin O titers (two consecutive tests at 2- to 4-week intervals) may be performed to help make the diagnosis. Special attention should be made to travel and exposure history to assess one's risk of associated infection. A chest radiograph should be considered in all patients with EN to assess for a possible underlying pulmonary process. In cases suspicious for tuberculosis, appropriate testing may include an intradermal tuberculin test or quantiferon gold testing. A full medical history and review of symptoms should be obtained to elucidate any signs or symptoms suggestive of underlying gastrointestinal disease (suggesting underlying inflammatory bowel disease), lung disease (suggesting

sarcoidosis or infectious pulmonary process), or constitutional symptoms (suggesting underlying malignancy).

A complete mucocutaneous and lymphatic examination should be completed with special attention to uncovering other cutaneous evidence of sarcoidosis (e.g., papular lesions of the knees or granulomatous infiltration of scars), Behçet's disease (oral and genital aphthae), Sweet disease (tender erythematous plaques), or malignancy (lymphadenopathy). A detailed review of the patient's medication list should be done to evaluate for any likely causative agents. Suspicion for a particular infectious etiology should be followed by appropriate diagnostic testing. Laboratory evaluation may reveal leukocytosis, elevated erythrocyte sedimentation rate, and elevated C-reactive protein. Only after all potential causative agents have been excluded may the diagnosis of idiopathic EN be made.

In cases in which the diagnosis cannot be rendered clinically, a skin biopsy may prove useful. The finding of septal (versus lobular) panniculitis helps to differentiate from other forms of panniculitis. A deep incisional biopsy with a depth adequate to include subcutaneous fat should be obtained. In early lesions, inflammation (predominantly neutrophilic) of the subcutaneous septa may be seen. In later lesions, there is characteristic widening and fibrosis of the septa (Fig. 15-2). Any stage of disease may show granulomatous features. Biopsy findings do not aid in determining underlying etiologic factors.

IV. TREATMENT Treatment of EN starts by eliminating any known causative agents. This may include discontinuing suspect medications after discussion with the prescribing physician. If an underlying disease process has been

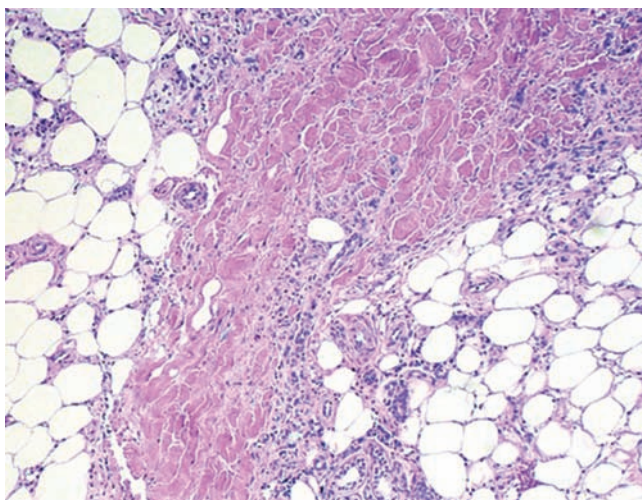


Figure 15-2. Histopathology of erythema nodosum demonstrating widening and fibrosis of the subcutaneous septa with surrounding inflammation. (Rubin R, Strayer DS. *Rubin's Pathology: Clinicopathologic Foundations of Medicine*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.)

identified, appropriate treatment for that condition should be initiated. In cases of Lofgren syndrome, systemic corticosteroids may be considered only after an infectious cause has been ruled out. Idiopathic disease is self-limited, and treatment strategies should focus on symptomatic management. Because the pain in EN is thought to occur as a result of edematous pressure on surrounding tissues, bed rest and leg elevation (legs raised above the level of the heart) should be advised. The use of compression stockings (15 to 20 mm Hg) is helpful, especially in patients who are more active (Table 15-2).

A. Nonsteroidal Anti-inflammatory Agents. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment for EN. These agents should be avoided or used with great caution in patients with renal disease, cardiovascular disease, or gastritis/esophagitis. Severe fetal defects, including premature ductus arteriosus closure, have been reported when these agents are used during pregnancy. Use of NSAIDs in the setting of Crohn disease may trigger a flare. Several NSAIDs are available, and the potential side effects of each should be considered when choosing the appropriate agent. Gilchrist and Patterson suggest initiating therapy with indomethacin and using ibuprofen or naproxen as second-line agents. Standard doses of NSAIDs are sufficient.

B. Potassium Iodide. Potassium iodide, which is thought to work by inhibiting neutrophil chemotaxis and release of toxic oxygen intermediates, may also be employed in the symptomatic treatment of EN. The typical starting dose for adults is 100 to 300 mg three times daily, with weekly titration up to 500 mg three times daily. It is administered as a saturated solution. The solution is very bitter and often leads to nausea, dysgeusia, excessive salivation, and gastrointestinal upset. The displeasing taste may be mitigated by diluting the solution with water, milk, juice, or cola. Serious side effects of potassium iodide include hypothyroidism with goiter formation. Patients may develop the Wolff-Chaikoff effect, where thyroid gland production of thyroid hormone ceases in the setting of excess iodine. Patients with underlying thyroid disease or those who are on certain medications (e.g., lithium, sulfonamides, amiodarone, and phenazone) are most predisposed to this adverse effect. Thyroid levels may be screened prior to and during therapy as appropriate. The potential for life-threatening potassium toxicity must

TABLE 15-2 Treatment Options and Differential Diagnosis	
Primary Treatment Options	
1. Rest, elevation, and compression	
2. Nonsteroidal anti-inflammatory drugs	
3. Potassium iodide	
4. Colchicine	
Differential Diagnosis	
• Erythema induratum (nodular vasculitis)	
• Pancreatic panniculitis	
• α 1-Antitrypsin deficiency panniculitis	
• Infection-induced panniculitis	

also be considered in patients who have renal disease, or patients taking potassium-sparing diuretics or angiotensin-converting enzyme inhibitors. Fatal pulmonary edema with cardiac failure has been reported with the use of this agent.

- C. Colchicine.** Through inhibition of microtubule polymerization necessary for neutrophil chemotaxis, colchicine may relieve symptomatic EN. Especially effective in women and in cases associated with Behçet's disease, colchicine doses of 1 to 2 mg daily (divided into twice-daily dosing) have been used. Gastrointestinal upset is the most common side effect and may be limited by slow dose titration. Bone marrow suppression with pancytopenia is a dose-dependent complication, most often reported with overdose.
- D. Corticosteroids.** In severe EN cases without underlying infection, the use of systemic corticosteroids may be considered. The patient should be engaged in a detailed discussion of the risk–benefit profile of this therapy prior to initiation of therapy. Intralesional corticosteroid injections (triamcinolone acetonide, 5 mg/mL) have been employed to facilitate individual lesion healing. Important risks of this treatment include systemic absorption as well as local tissue atrophy and dyspigmentation.
- E. Other Treatments.** Reports of treatment success with tetracyclines and hydroxychloroquine exist, although data are limited.

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Suggested Readings

- Davis MD. Response of recalcitrant erythema nodosum to tetracyclines. *J Am Acad Dermatol.* 2011;64:1211-1212.
- Gilchrist H, Patterson JW. Erythema nodosum and erythema induratum (nodular vasculitis): diagnosis and management. *Dermatol Ther.* 2010;23:320-327.
- Mana J, Marcoval J. Erythema nodosum. *Clin Dermatol.* 2007;25:288-294.
- Papagrigoraki A, Gisondi P, Rosina P, et al. Erythema nodosum: etiological factors and relapses in a retrospective cohort study. *Eur J Dermatol.* 2010;20:773-777.
- Requena L, Sanchez Yus E. Erythema nodosum. *Dermatol Clin.* 2008;26:425-438.
- Schwartz RA, Nervi SJ. Erythema nodosum: a sign of systemic disease. *Am Fam Physician.* 2007;75:695-700.

16

Fungal Infections

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CANDIDIASIS

I. BACKGROUND *Candida albicans*, a normal inhabitant of mucous membranes, skin, and the gastrointestinal tract, can evolve from a commensal organism to a pathogen causing mucocutaneous infection. Factors that predispose to infection include (i) a local environment of moisture, warmth, and occlusion; (ii) systemic antibiotics, corticosteroids and other immunosuppressive agents, or birth control pills; (iii) pregnancy; (iv) diabetes; (v) Cushing disease; and (vi) debilitated states. Immune reactivity to *Candida* is reduced in infants up to 6 months of age and in patients with lymphoproliferative diseases or acquired immunodeficiency syndrome. However, most women with recurrent vulvovaginal candidiasis have normal cellular immunity. Recently, nonalbicans *Candida* strains have been recognized as an important pathogen, particularly in recurrent infections.¹

The resident bacteria on skin inhibit the proliferation of *C. albicans*. Cell-mediated immunity plays a major role in the defense against infection. In addition, *C. albicans* can activate complement through the alternative pathway. The innate immune system appears to respond to mannan, a *C. albicans* cell wall polysaccharide, through toll-like receptors 2 and 4.²

II. CLINICAL PRESENTATION

1. Paronychia (Fig. 16-1) is associated with rounding and lifting of the proximal nail fold, disruption of the cuticle, and erythema and swelling of the fingertip. The nail plate may display transverse ridging or greenish-brown discoloration. In chronic paronychia, the area surrounding the nail is tender, and there is often a history of frequent wetting of the hands.
2. Intertriginous lesions (inframammary, axillary, groin, perianal, and interdigital) (Figs. 16-2 and 16-3) are red, macerated, and sometimes fissured. The lesions are well demarcated, with peeling borders, and often surrounded by satellite erythematous papules or pustules.
3. The white plaques of thrush can be scraped from mucous membranes with a tongue blade, in contrast to the fixed lesions of oral hairy leukoplakia. The underlying mucosa is bright red. Lesions may extend into the esophagus. The discomfort of oropharyngeal candidiasis may interfere with eating.
4. Perleche or angular cheilitis (Fig. 16-4) presents with fissured erythematous moist patches at the angles of the mouth. Poorly fitting dentures or mouth breathing may be associated.
5. *Candida* vulvovaginitis is frequently associated with a vaginal discharge. There may be severe vulvar erythema, edema, and pruritus.



Figure 16-1. Chronic paronychia. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 16-2. Cutaneous candidiasis of the groin: Bright red plaque with peripheral satellite pustules. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

III. WORKUP

1. Direct examination of scrapings from lesions with potassium hydroxide (KOH) will reveal budding yeasts with or without hyphae or pseudohyphae (Fig. 16-5). Hyphae are almost always seen in mucous membrane infection,



Figure 16-3. Cutaneous candidiasis of the diaper area: Bright red confluent plaque with peripheral satellite pustules in a 1-year-old child after a course of oral antibiotics. (From Owen Laboratories, Inc. Sauer GC, Hall JC. *Manual of Skin Diseases*. 7th ed. Philadelphia, PA: Lippincott-Raven;1996.)



Figure 16-4. Perleche: Erythema and fissuring at the angles of the mouth due to salivary pooling and maceration. *Candida* often is secondary infection in these folds. This may be common in edentulous persons or those with ill-fitting dentures. (From Neville B, Damm CD, White OK, et al. *Color Atlas of Clinical Oral Pathology*. Philadelphia, PA: Lea & Febiger; 1991.)

but may be absent in skin infection. A rapid latex agglutination test is also available for diagnosis but offers little advantage over KOH in terms of sensitivity and specificity.³

2. *Candida albicans* grows readily within 48 to 72 hours on fungal or bacterial media. Specific identification is based on the presence of chlamydospores when the organism is subcultured on cornmeal agar.

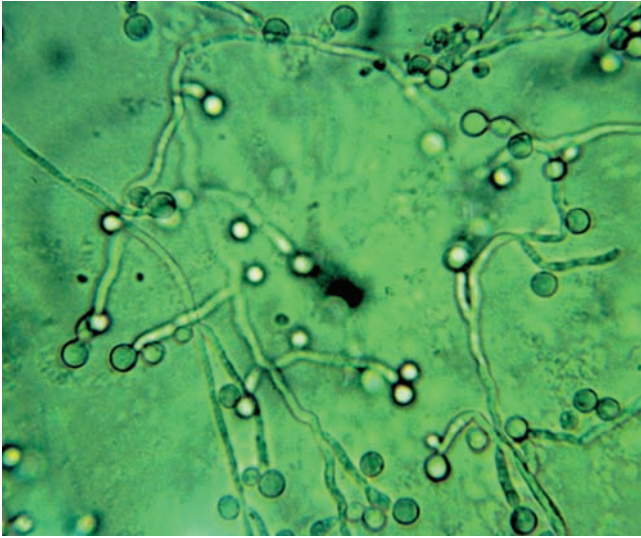


Figure 16-5. Potassium hydroxide (KOH) examination of *Candida*: Pseudohyphae with budding spores. (From Goodheart HP: *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

3. Gram stain and culture of affected areas can be helpful. Gram-negative rods may play a synergistic role in infection of intertriginous areas.

IV. TREATMENT The imidazoles (ketoconazole, miconazole, clotrimazole, and econazole) and broader-spectrum triazoles (fluconazole, itraconazole, voriconazole, and posaconazole) are used most often in the treatment of candidal infections (Table 16-1). The pyridone derivative ciclopirox (Loprox) and the polyene antibiotic nystatin are also effective. The allylamines naftifine (Naftin) and terbinafine (Lamisil) and the benzylamine butenafine (Mentax) are fungistatic against *Candida*. Tolnaftate (Tinactin) and undecylenic acid (Cruex; Desenex) are NOT effective against *Candida*.

Systemic treatment of vaginal infections has become widespread. Oral imidazoles and triazoles are also useful in chronic mucocutaneous candidiasis and recalcitrant candidal onychomycosis. Ketoconazole and, to a lesser degree, itraconazole have many drug–drug interactions owing to the inhibition of cytochrome P-450 3A4. Their use is contraindicated with simvastatin, lovastatin, cisapride, triazolam, midazolam, quinidine, dofetilide, and pimozide.⁴

A. Paronychia. Successful treatment of a chronic paronychia often requires weeks to months, and nails will grow out normally within 3 to 6 months of the paronychia healing.

1. **An imidazole**, such as ketoconazole (Nizoral), sertaconazole (Ertaczo), clotrimazole (Lotrimin, Mycelex), miconazole, or ciclopirox olamine (Loprox), should be applied several times a day. Other effective agents include naftifine (Naftin), haloprogin (Halotex), or nystatin.

TABLE 16-1 Top Treatment Choices for Candidal Infections

Topicals		
Imidazoles	Clotrimazole Miconazole Econazole Ketoconazole	Various preparations and regimens (see text)
Polyenes	Nystatin	Cream, ointment, powder, troches, and intravaginal preparations
Pyridone-derivative	Ciclopirox	Cream, gel, and solution
Allylamines (fungistatic)	Naftifine Terbinafine	Cream and gel Less effective against <i>Candida</i> than azoles
Orals		
Imidazoles	Ketoconazole	Higher risk of drug–drug interaction
Triazoles	Fluconazole Itraconazole	150 mg PO × 1; various regimens Higher risk of drug–drug interaction

If there is associated pain or edema, use a combined steroid–nystatin ointment (e.g., Mycolog II) or a topical corticosteroid cream along with the antifungal agent for the first several days. Overnight application under occlusion may increase effectiveness. Oral therapy may be helpful as well. In addition, the area should be protected during wet work by wearing waterproof gloves and cotton liners.

- 2. **Two to Four Percent Thymol in Chloroform or Absolute Alcohol** is a simple and effective alternative that is applied b.i.d. to t.i.d.
- 3. **Amphotericin B (Fungizone) Lotion or Cream or 1% Alcoholic Solution of Gentian Violet** may also be used. Because amphotericin B and imidazole agents counteract one another, they should not be used simultaneously.

B. Intertriginous Lesions

- 1. **Education** about the role of moisture and maceration is important. The following techniques may be recommended: (i) drying affected areas after bathing using a handheld hair dryer on low heat, at least once a day; (ii) supportive clothing and weight reduction; (iii) air conditioning in warm environments; and (iv) regular application of a plain or medicated powder (nystatin or miconazole) to the areas.
- 2. **For Very Inflammatory Lesions**, open compresses three to four times a day with water or Burow solution (Domeboro) will expedite relief of symptoms.
- 3. **A Topical Antifungal Cream or Nystatin or Miconazole Powder** should be applied to the dried skin.
- 4. **Gentian Violet 0.25% to 2.0% and Castellani Paint** (fuchsin, phenol, and resorcinol) are older remedies, which are effective but may sting and will stain clothing, bed linen, and skin.

C. Thrush

1. **Clotrimazole Buccal Troches** (10 mg) five times a day for 2 weeks are usually effective for oropharyngeal candidiasis in adults and older children. The dose for infants has not been well established.
2. **Alternatively, Nystatin Oral Suspension** (400,000 to 600,000 units) q.i.d. is held in the mouth for several minutes before swallowing. The dosage for infants is 2 mL (200,000 units) q.i.d.
3. **Oral fluconazole** (50 mg daily) has been the mainstay of systemic therapy in the past.⁵ However, with frequent use in immunocompromised hosts, fluconazole-resistant candidiasis has been reported. In this situation, itraconazole 200 mg PO q.d. for 2 to 4 weeks may prove effective.⁴ Voriconazole may also be useful.⁶ Anidulafungin, a member of the novel class of antifungals, echinocandins, is equal in efficacy to fluconazole in the treatment of esophageal candidiasis, has few significant drug–drug interactions, and is well tolerated.⁷
4. **Amphotericin B** (80 mg/mL) may be used as a rinse.
5. **Gentian Violet Solution** 1% to 2% may be tried in difficult or recurrent cases.

D. Vulvovaginitis

1. **Imidazoles or Triazoles** are the first-line drugs. Fluconazole has the least potential for drug interactions and is considered the least toxic.
2. **Resistance to Therapy** may be due to infection with nonalbicans strains such as *Candida glabrata* and *Candida tropicalis*.
3. **Topical Therapies**
 - a. **Imidazole compounds** are effective and are available in a wide array of formulations: 500 mg clotrimazole vaginal tablet as a single dose (Gyne-Lotrimin), 200 mg miconazole tablet at bedtime for 3 days (Monistat-3), 100 mg vaginal tablet or suppository at bedtime for 7 days (Gyne-Lotrimin, Mycelex, Monistat-7), 2% butoconazole (Gynazole, Femstat) or miconazole (Monistat-7) cream daily at bedtime for 3 to 7 days, or 1% miconazole cream for 7 to 14 days (Gyne-Lotrimin, Mycelex). Prophylactic treatment may be helpful in chronic infection. Miconazole is pregnancy category C and clotrimazole is a category B medication.
 - b. **Terconazole (Terazol)** is a fungicidal triazole topical preparation effective against many *Candida* strains. It is used as either a 3-day or a 7-day course (Terazol 7—0.4% cream for 7 days, or Terazol 3—0.8% cream for 3 days). Terconazole is pregnancy category C and is not recommended for use during the first trimester.
 - c. **Nystatin Vaginal Suppositories** (100,000 units) may be slightly less effective. They are dosed twice daily for 7 to 14 days and then nightly for an additional 2 to 3 weeks. Topical nystatin is pregnancy category A.
 - d. **Boric Acid**, 600 mg in a gelatin capsule, used intravaginally daily for 14 days has been reported effective even in resistant *Candida* infections. It may cause local irritation or toxicity from systemic absorption.
 - e. **In Severe or Very Symptomatic *Candida* Vulvitis**, a topical corticosteroid for the first 3 to 4 days may be used.
4. **Systemic Therapies**
 - a. **A Single Oral Dose of 150 mg of fluconazole** has been U.S. Food and Drug Administration (FDA) approved for the treatment of vaginal candidiasis. Its efficacy is equivalent to topical therapy and to

oral itraconazole 200 mg at two doses 12 hours apart.⁸ Slightly greater efficacy may be achieved with fluconazole 100 mg/day for 5 to 7 days or itraconazole 200 mg/day for 3 to 5 days.⁹

b. In a randomized controlled trial, neither oral nor intravaginal use of yogurt-containing *Lactobacillus acidophilus* was shown to decrease candidal infection.¹⁰

c. Recurrent infection is defined as greater than three episodes per year in the absence of antibiotic use. Prophylactic regimens include clotrimazole (Gyne-Lotrimin) two 100-mg tablets intravaginally BIW, terconazole (Terazol) 0.8% cream one applicator per week, and fluconazole (Diflucan) 150 mg PO each week.¹¹

In addition to treating the *Candida* infection, it is important to address predisposing medical conditions and physical factors. Diabetic patients must pay attention to blood sugar levels. Those patients with recurrent vulvovaginal candidiasis should avoid spermicide. As with all conditions, a careful history and physical examination must be performed.

ONYCHOMYCOSIS

I. BACKGROUND Onychomycosis, or fungal infection of the nails, is seen in approximately 6% to 8% of the adult population, and in 40% of patients with fungal infections in other locations. It is the most common nail disorder, accounting for approximately half of all nail abnormalities. Clinical subtypes of infection include distal lateral subungual, proximal subungual, white superficial, and candidal onychomycosis. Risk factors for dermatophyte infections include aging, humid or moist environments, psoriasis, tinea pedis, injured or damaged nails, and immunocompromised states. Fingernails are less commonly involved than toenails. Dermatophytes such as *Trichophyton* species, *Epidermophyton*, and *Microsporum* are the most common causes of onychomycosis; however, *Candida* and nondermatophyte molds such as *Scopulariopsis brevicaulis*, *Fusarium* sp., *Acremonium*, and *Aspergillus* species can also cause infection.

II. CLINICAL PRESENTATION In onychomycosis, nails become brittle, friable, and thickened (Fig. 16-6). Patients are often disturbed by the appearance of their nails, and they may report nail tenderness. In distal subungual infection, changes are first seen at the free margin or distal lateral border of the nail as a white or yellow discoloration. The nail changes progress proximally becoming thickened, crumbly, and elevated by accumulated subungual debris. In some cases, the nail plate becomes entirely replaced by this keratinaceous debris. In white superficial onychomycosis, fungus invades the superficial layers of the nail plate to form “white islands” on the nail plate. In proximal subungual onychomycosis, fungus directly penetrates the nail plate through the proximal nail fold.

III. WORKUP Definitive diagnosis is made by the microscopic identification of hyphae in nails or subungual debris treated with KOH (Fig. 16-7). Histologic evaluation of nails using a periodic acid–Schiff stain and fungal culture of nail clippings may also be useful when no hyphae are seen on KOH



Figure 16-6. A dystrophic, discolored nail with subungual hyperkeratosis under the great toe typical of onychomycosis. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

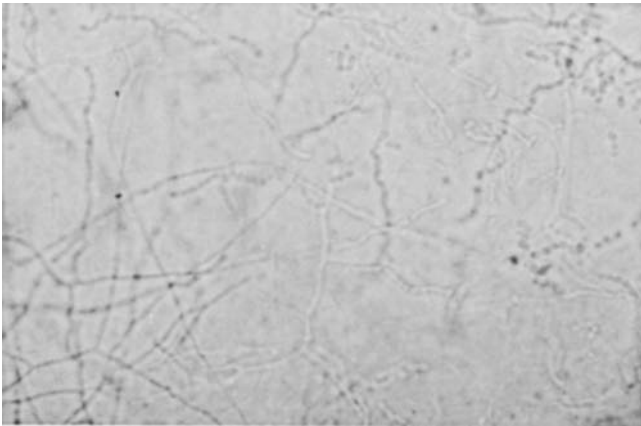


Figure 16-7. KOH preparation showing dermatophyte hyphae. (Courtesy of Victor Newcomer, MD, Santa Monica, CA.)

but the clinical suspicion for onychomycosis remains high. Culture results may also be beneficial in selecting appropriate therapies.

IV. TREATMENT Treatment of onychomycosis can be challenging. Nails grow at a slow rate, and recurrence of disease is common (Table 16-2). Further information on the drugs and devices commonly used for onychomycosis treatment are described in following pages.

TABLE 16-2 Oral Treatment Options for Onychomycosis (Toenails)

- 1. Terbinafine (250 mg q.d. for 12 wk)
- 2. Itraconazole (pulse therapy of 200 mg b.i.d. for 1 wk each month for 3 mo)
- 3. Fluconazole (200–400 mg qwk for 6 mo)

A. Topical Therapy. Topical medications for onychomycosis are often unable to fully penetrate the nailplate, and, therefore, complete fungal eradication with these medications alone is difficult. For example, ciclopirox solution, 8%, in a nail lacquer formulation (Penlac) applied daily to the entire nail and surrounding skin has a clinical cure rate of only 5.5% after 48 weeks of therapy. Naftifine (Naftin), terbinafine (Lamisil), and ciclopirox (Loprox) creams similarly have low efficacy. Two recent studies of efinaconazole 10% solution, a triazole antifungal developed for distal lateral subungual onychomycosis (DLSO), showed complete cure rates of 17.8% and 15.2% after 48 weeks of use in patients with DLSO, suggesting that this medication may be more efficacious than other topical treatments.¹² Chemical or surgical nail avulsion may also be beneficial in the treatment of onychomycosis and should be considered an adjunctive treatment in patients undergoing topical and/or oral therapy.

B. Systemic Therapy. Oral therapy is an especially important consideration in onychomycosis given the poor success rates of most topical therapies. Terbinafine (Lamisil), a second-generation allylamine, is considered the treatment of choice for onychomycosis. It is well absorbed and rapidly delivered to the stratum corneum and nails. The recommended treatment dose is 250 mg q.d. for 6 weeks for fingernails and for 12 weeks for toenails, with adjustments made for patients with kidney or liver failure. Adverse effects are rare. Gastrointestinal disturbance (4.9%), taste disturbance, cutaneous eruptions including (rarely) Stevens-Johnson syndrome/toxic epidermal necrolysis, hepatobiliary dysfunction, visual disturbance, and rare hematologic disturbance including neutropenia are possible. Liver function testing is recommended in patients treated for longer than 6 weeks. Liver enzyme abnormalities are typically asymptomatic and reversible. Drug interactions occur with other medications metabolized through the cytochrome P-450 system. Commonly affected medications include rifampin, cimetidine, terfenadine, caffeine, and cyclosporine.

Itraconazole (Sporanox) is also effective in treating onychomycosis. Treatment with pulse therapy using 200 mg b.i.d. for 1 week out of each month may be used instead of continuous therapy.¹³ It is also effective in onychomycosis caused by nondermatophyte molds.¹⁴ Two monthly pulses are recommended for fingernails and three pulses for toenails. Itraconazole is metabolized by the cytochrome P-450 system and may increase the levels of warfarin, cyclosporine, and digoxin among others. Its use is contraindicated with certain medications. Adverse effects include nausea, vomiting, and elevated aminotransferase levels in 5% to 10% of patients. Monitoring of liver function tests is recommended if therapy exceeds 6 weeks.

Fluconazole (Diflucan), a triazole, may also be effective in onychomycosis. It has good oral absorption, is well tolerated, and is preferentially taken up in

keratinized tissues. Recommended doses for onychomycosis are 200 to 400 mg qwk for 3 months for fingernails and for 6 months for toenails.

C. Device-Based Therapy. Device-based therapies are a rapidly expanding area of onychomycosis treatment. The long duration of therapy, high relapse rates, and adverse effects seen with many onychomycosis pharmacotherapies have contributed to this expansion. Lasers are one of such devices that have gained FDA approval for the treatment of onychomycosis. Although the exact mechanism by which lasers treat onychomycosis is unknown, they are thought to have a fungicidal effect by exploiting the sensitivity of fungi to temperatures over 55°C.^{15,16} Both the neodymium-doped yttrium aluminum garnet (Nd:YAG) laser and diode laser are approved by the FDA for onychomycosis treatment; however, evidence-based data on the efficacy of these lasers are poor.

Photodynamic therapy (PDT) is also being investigated for the treatment of onychomycosis. PDT uses a spectrum of visible light to activate a topically applied photosensitizing agent, generating reactive oxygen species and inducing apoptosis. Several clinical trials have tested the efficacy of the heme biosynthesis intermediates 5-aminolevulinic acid and methyl aminolevulinate as photosensitizers for treating onychomycosis. Further studies are necessary to determine the exact clinical efficacy of this treatment method.

Iontophoresis uses a low-level electrical current to increase drug transport across a semipermeable barrier. Combining this technique with terbinafine therapy may optimize terbinafine's penetration of the nail bed and matrix, leading to higher cure rates of onychomycosis. Clinical trials on such devices are currently underway.

TINEA CAPITIS

I. BACKGROUND Tinea capitis is a dermatophyte infection of the scalp and hair shaft. It is the most common fungal infection in children worldwide, commonly seen in children between the ages of 3 and 7 years old.¹⁷ It is acquired by close contact with an infected person or use of an infected person's hair brush. It is seen often in crowded urban environments within the same household. The two organisms most commonly responsible for tinea capitis are *Trichophyton tonsurans*, which is acquired from humans and *Microsporum canis*, which is acquired from animals. Tinea capitis is one of the most common causes of acquired circumscribed hair loss.

II. CLINICAL PRESENTATION There are four clinical manifestations of tinea capitis:

- The seborrheic dermatitis type is the most common type that appears as white, patchy areas of hair loss and broken hairs with scaling and hyperkeratosis.
- The inflammatory or kerion type is a more serious host response to dermatophyte infection that presents with painful, inflamed follicles that can lead to a boggy scalp mass. Kerions can lead to scarring alopecia.
- The black dot pattern is named after the hairs that are weakened by infection and break off on the surface of the scalp.
- The pustular type appears as areas of the scalp with pustules or scabbed areas without alopecia.

III. WORKUP Diagnosis can be made via clinical presentation and a thorough history. For confirmation, infected hairs and skin scrapings should be examined on a KOH wet mount. The identification of hyphae under KOH wet mount confirms diagnosis. If negative, fungal cultures may be sent for a definitive diagnosis. Woods lamp examination is useful if fluorescent *Microsporum* species are suspected as the pathogen.

IV. TREATMENT Topical treatments cannot penetrate the hair shafts and are therefore not used for complete resolution of tinea capitis. Instead, systemic antifungal medications are used because they can penetrate the hair follicles. A 6-week course of oral griseofulvin is considered first-line treatment, but 2- to 4-week courses of oral terbinafine, itraconazole, or fluconazole are also effective treatment of tinea capitis (Table 16-3).¹⁸ Shampoos, such as 2% selenium sulfide and ketoconazole, are sporicidal and may be used in addition to oral antifungals to prevent spread of infection. Oral steroids may be needed for cases of severe inflammation. To prevent reinfection, all hair brushes should be replaced and all bedding and clothing should be washed in hot water.

TINEA BARBAE

I. BACKGROUND Tinea barbae is a dermatophyte infection of the beard and mustache area. There are two types of tinea barbae and they are caused by different pathogens. The ringworm pattern is most commonly caused by *Trichophyton rubrum* or *Trichophyton violaceum*. The follicular pattern is normally caused by *Trichophyton mentagrophytes* and *Trichophyton verrucosum*.

II. CLINICAL PRESENTATION Infection usually starts in a small section of the beard with infected follicles and develops into a more extensive infection.

- The ringworm pattern has circular, erythematous, and scaly plaques with sharply defined borders.

TABLE 16-3 Treatment for Tinea		
Infection	Recommended First-Line Treatment	Recommended Alternative Treatment (Adult)
Tinea capitis	Griseofulvin 500 mg/d (20–25 mg/kg/d) PO for 6–8 wk ⁵	Terbinafine 250 mg/d (3–6 mg/kg/d) PO for 2–4 wk ⁵
Tinea barbae	Terbinafine 250 mg/d PO for 2–4 wk ⁵	Itraconazole 200 mg PO for 2–4 wk ⁵
Tinea pedis	Terbinafine 1% cream for 1–4 wk or until resolution of symptoms ⁵	Griseofulvin 500 mg/d (25 mg/kg/d) PO for 6–12 wk for resistant infections ⁵
Tinea cruris	Clotrimazole 1% cream for 4 wk ⁵	Itraconazole 200 mg/d PO for 1–2 wk for resistant infections ⁵

- The follicular pattern is a deeper infection with pustules and boggy kerions that can lead to scarring. The local lymph nodes may be inflamed if secondary bacterial infection has occurred.¹⁹

III. WORKUP Clinical presentation and a thorough history may lead to diagnosis, as removal of affected hair is painless with tinea barbae. To confirm diagnosis, hair and skin scrapings should be examined on a KOH wet mount to identify hyphae. Fungal cultures also may be considered if results are inconclusive.

IV. TREATMENT Topical antifungal agents are generally not used for tinea barbae because they do not penetrate the infected follicle. A 4-week course of oral griseofulvin, a 2- to 4-week course of oral terbinafine or itraconazole, and a 3- to 4-week course of fluconazole are standard treatments (Table 16-3).¹⁹ Topical steroids may be used to reduce pruritus and oral steroids may be necessary if the infection is deep, with severe inflammation.

TINEA PEDIS

I. BACKGROUND Tinea pedis is a dermatophyte infection of the feet, which is commonly known as athlete's foot. It tends to occur almost exclusively in adults. Three dermatophytes may cause tinea pedis: *Trichophyton* sp., *Epidermophyton* sp., or *Microsporum* sp., with *T. rubrum* as the most common pathogen. Infection is spread by humans, animals, or soil. Moist environments, such as wet socks, public showers, and pools, tend to spread infection. Patients who are elderly, obese, and diabetic are at increased risk for infection.

II. CLINICAL PRESENTATION Tinea pedis has three types, based on the location in different regions of the feet. Cellulitis is a potential complication of all three types.

- If the infection is found between the toes, it is called the interdigital tinea pedis, the most common type. It typically is found in the digit interspaces of the fourth and fifth toes. Patients complain of itching, burning, scaling, and malodor. In patients who are immunocompromised, fissuring of the interspaces, hyperkeratosis, and erosions can occur, leading to bacterial infection.
- The moccasin type of infection is located on the lateral aspects and bottom of the foot. It is often found bilaterally, and the patients tend to have scaly, erythematous, and hyperkeratotic areas. Occasionally, papules will be located along the erythematous border.²⁰
- Vesiculobullous type is a less common variant that presents with vesicles and bullae on the plantar surfaces of the feet.

III. WORKUP Diagnosis can be made by taking a thorough history and examining skin scrapings on a KOH wet mount. The identification of hyphae under KOH wet mount confirms diagnosis. Occasionally, cultures are required if the wet mount is negative. Examination with a Wood lamp may be necessary to rule out fluorescing *Microsporum* species.

IV. TREATMENT Patients should keep their feet dry with foot powder and should wear nonocclusive footwear. To prevent the spread of infection, patients

should not go barefoot in public areas. Antifungal powders are useful for the interdigital type of tinea pedis. Four weeks of topical antifungal creams such as butenafine, ketoconazole, econazole, and ciclopirox are normally effective, but oral griseofulvin, itraconazole, fluconazole, or terbinafine may be needed for more resistant or serious infections (Table 16-3). Topical steroids may reduce pruritus and oral steroids may be necessary if the infection is deep with severe inflammation.

TINEA CRURIS

- I. BACKGROUND** Tinea cruris is a dermatophyte infection of the groin and upper thighs often referred to as “jock itch” (Fig. 16-8). It is commonly seen in adolescent males who play sports and in overweight individuals who wear tight pants.²¹ Coinfection with tinea pedis is seen because *T. rubrum* may be the causative agent of both. Infection is passed on by person-to-person contact. The fungus thrives in the crural folds, particularly with excessive sweating.
- II. CLINICAL PRESENTATION** Pruritic, erythematous, raised-brown patches with sharply defined borders are seen on the groin and inner thighs bilaterally. Vesicles may form along the edge of the rash. The infection may migrate to the gluteal cleft and buttocks, but the scrotum and penis are not normally affected.
- III. WORKUP** Clinical presentation and a thorough history may be sufficient for diagnosis, especially if the patient has coinfection with tinea pedis. For a diagnosis of the causative agent, skin scrapings from the edge of the rash may be examined on a KOH wet mount for hyphae. If the wet mount is negative, a culture may be taken for definitive diagnosis.



Figure 16-8. Tinea cruris. (Image provided by Stedman's.)

IV. TREATMENT Keep skin clean and dry, wear loose clothing, and wash all clothes in hot water. Treatment of the rash with topical antifungal creams, such as clotrimazole, butenafine, miconazole, or tolnaftate is standard (Table 16-3). Medication should be applied to the affected area twice a day for at least 2 weeks, or until a week after the rash has disappeared. The cream should be applied to the rash and also 2 cm outside the border of the rash to ensure complete coverage. If the infection is resistant to topical therapy, then oral itraconazole, fluconazole, or terbinafine may be used.¹⁹

TINEA VERSICOLOR

I. BACKGROUND Tinea versicolor is a chronic superficial fungal infection caused by members of the fungal genus *Malassezia* (*Pityrosporum*), which are considered normal skin flora. Environmental and immunologic changes may cause conversion of the yeast form to the hyphal form leading to pigmentary changes in the skin. The most common causative agents are *Malassezia globosa* followed by *Malassezia furfur*. The eruption is found worldwide, is seen most commonly in young adults in temperate zones, and accounts for approximately 5% of all fungal infections. Factors predisposing to clinical infection are found in Table 16-4.

Tinea versicolor has a unique propensity to present either hyper- or hypopigmented lesions. Table 16-5 summarizes the pathogenesis of the lesions.

II. CLINICAL PRESENTATION The eruption is usually asymptomatic, although some patients complain of mild pruritus. Patients tend to be more concerned with cosmesis or potential for transmission to others. Lesions vary in color from white and pink to light-brown or fawn-colored. Typical early presentation consists of many, 3 to 5 mm, round or oval macules with a fine superficial scale. As the eruption progresses, the lesions tend to coalesce producing irregularly shaped, “moth-eaten,” patches and plaques (Figs. 16-9 and 16-10). The eruption occurs most commonly on the upper trunk and neck,

TABLE 16-4 Factors Predisposing to Tinea Versicolor

Warm, humid climate
Exposure to sunlight
Genetic predisposition
Immunosuppression
Hyperhidrosis
Pregnancy
High plasma cortisol (as in patient taking systemic corticosteroids)
Malnutrition
Application of topical steroids
Application of topical oils or oily creams

TABLE 16-5 Pathogenesis of Hypo- and Hyperpigmented Lesions in Tinea Versicolor	
Hypopigmented lesions	<ul style="list-style-type: none">• <i>Malassezia</i> species produces azelaic acid, which inhibits the enzyme responsible for melanin production• Histologically, melanosomes are smaller than normal, and no inflammatory infiltrate is evident
Hyperpigmented lesions	<ul style="list-style-type: none">• Pathogenesis remains unknown• Histologically, there is an increased number of larger than normal melanosomes, and a thicker keratin layer with more organisms present



Figure 16-9. Tinea versicolor: This figure shows hyperpigmented, fawn-colored lesions coalescing on the back. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 16-10. Tinea versicolor: This figure shows hypopigmented lesions. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

but may be more widespread if allowed to progress. The face is rarely involved, but when affected, lesions are seen more often on the forehead. Facial lesions occur more commonly in children, and when seen in adults, women are affected more than men. Patients usually present during summer months when the hypopigmented lesions are accentuated by tanning of surrounding normal skin.

III. WORKUP Table 16-6 summarizes the diagnostic approach (Fig. 16-6).

IV. TREATMENT Treatment options for tinea versicolor are abundant. Topical antifungal therapy is usually sufficient, but in more widespread disease, systemic therapy may be preferred. However, systemic therapy may be contraindicated in some situations such as in patients with a history of liver disease or

TABLE 16-6 Diagnostic Approach	
Technique	Finding/Comments
KOH preparation	<ul style="list-style-type: none">• Numerous short, thick, straight, and curved hyphae (spaghetti) as well as clusters of thick-walled, round, and budding yeast (meatballs) (Fig. 16-11)
Fungal culture	<ul style="list-style-type: none">• Typically not necessary for diagnose, but if done, lipid-enriched media must be used
Wood light examination	<ul style="list-style-type: none">• Intensifies visualization of pigmentary changes• Affected areas may show yellow-green fluorescence

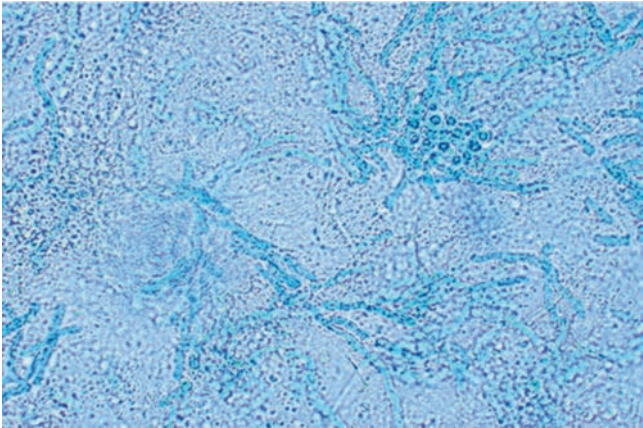


Figure 16-11. Potassium hydroxide (KOH) preparation of tinea versicolor showing many short, wavy hyphae (spaghetti) and clusters of spores (meatballs). (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

excessive alcohol consumption. Additionally, systemic agents are more likely to cause side effects, including gastrointestinal upset, elevated liver enzymes, headache, and rash. Finally, when taken orally, the imidazole agents are metabolized by the cytochrome P-450 system in the liver, and thus, have the potential for interaction with many other medications.

Topical treatments should be applied to the entire torso from the neck to the waist, because lesions may be widespread as well as clinically unapparent. Although the appearance of the rash will improve within days, patients should be counseled that it may take months for pigmentary changes to resolve. Relapse or reinfection is common, and in such cases, continued weekly therapy for several months or longer may be helpful. Table 16-7 provides a summary of topical therapy for tinea versicolor, while Table 16-8 summarizes systemic options.

TABLE 16-7 Topical Therapies			
	Generic (Trade) Name	Dosage	Comments
Topical shampoos	Ketoconazole 2% (Nizoral) shampoo	Applied to the scalp or skin daily for 14 d, left on for 5–10 min, and then rinsed off	
	Selenium sulfide (Selsun Blue) suspension	Applied to the scalp or skin daily for 14 d, left on for 5–10 min, and then rinsed off	
	Ciclopirox (Loprox) shampoo	Applied to the scalp or skin daily for 14 d, left on for 5–10 min, and then rinsed off	
	Zinc pyrithione (Head and Shoulders) shampoo	Applied to the scalp or skin daily for 14 d, left on for 5–10 min, and then rinsed off	
Topical antifungals	Imidazole creams	Applied to the affected area once or twice daily for 1–4 wk	The imidazole antifungal creams include ketoconazole, bifonazole, miconazole, econazole, and clotrimazole
	Allylamine creams	Applied to the affected area once or twice daily for 1–4 wk	The allylamine creams include naftifine and terbinafine

TABLE 16-7 (Continued)

	Ciclopirox cream	Applied to the affected area once or twice daily for 1–4 wk	
	Tolnaftate cream	Applied to the affected area once or twice daily for 1–4 wk	Other formulations: aerosol spray, liquid, solution, and powder
	Haloprogin cream	Applied to the affected area once or twice daily for 1–4 wk	
Other topical therapies	<ul style="list-style-type: none"> • Salicylic acid preparations • Benzoyl peroxide preparations • Sulfur preparations 		

TABLE 16-8 Systemic Therapies

Generic Name	Dosage	Additional Information
Ketoconazole	• 200 mg daily for 10 d	Single dose regimens (400 mg taken once) may be less effective
Itraconazole	<ul style="list-style-type: none"> • 200 mg daily for 5–7 d • 100 mg daily for 14 d 	A shorter duration regimen (400 mg daily for 3 d) may also be effective, but single dose regimens (400 mg taken once) have been shown to be less effective
Fluconazole	• 200–400 mg weekly for 2–4 wk	Single dose regimens (400 mg taken once) may be less effective

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REFERENCES

1. Richter SS, Galask RP, Messer SA, et al. Antifungal susceptibilities of *Candida* species causing vulvovaginitis and epidemiology of recurrent cases. *J Clin Microbiol.* 2005;43(5):2155–2162.
2. Roeder A, Kirschning CJ, Rupec RA, et al. Toll-like receptors and innate antifungal responses. *Trends Microbiol.* 2004;12(1):44–49.

3. Reed BD, Pierson CL. Evaluation of a latex agglutination test for the identification of *Candida* species in vaginal discharge. *J Am Board Fam Pract.* 1992;5 (4):375-380.
4. Huang DB, Ostrosky-Zeichner LO, Wu JJ, et al. Therapy of common superficial fungal infections. *Dermatol Ther.* 2004;17:517-522.
5. Hay RJ. The management of superficial candidiasis. *J Am Acad Dermatol.* 1999;40: S35-S42.
6. Kofla G, Ruhnke M. Voriconazole: review of a broad spectrum triazole antifungal agent. *Expert Opin Pharmacother.* 2005;6(7):1215-1229.
7. Vasquez JA. Anidulafungin: a new echinocandin with a novel profile. *Clin Ther.* 2005;27(6):657-673.
8. Edelman DA, Grant S. One-day therapy for vaginal candidiasis. *J Reprod Med.* 1999;44: 543-547.
9. Mikamo H, Kawazoe K, Sato Y, et al. Comparative study on the effectiveness of antifungal agents in regimens against vaginal candidiasis. *Chemotherapy.* 1998;44:364-368.
10. Pirodda M, Gunn J, Chondros P, et al. Effect of lactobacillus in preventing post-antibiotic vulvovaginal candidiasis: a randomised controlled trial. *BMJ.* 2004;329(7465):548.
11. Sobel JD, Wiesenfeld HC, Martens M, et al. Maintenance fluconazole therapy for recurrent vulvovaginal candidiasis. *N Engl J Med.* 2004;351(9):876-883.
12. Elewski BE, Rich P, Pollack R, et al. Efinaconazole 10% solution in the treatment of toenail onychomycosis: two phase III multicenter, randomized, double-blind studies. *J Am Acad Dermatol.* 2013;68 (4):600-608.
13. Huang DB, Ostrosky-Zeichner LO, Wu JJ, et al. Therapy of common superficial fungal infections. *Dermatol Ther.* 2004;17:517-522.
14. De Doncker PR, Scher RK, Baran RL, et al. Itraconazole therapy is effective for pedal onychomycosis caused by some nondermatophyte molds and in mixed infection with dermatophytes and molds: a multicenter study with 36 patients. *J Am Acad Dermatol.* 1997;36:173-177.
15. Hashimoto T, Blumenthal HJ. Survival and resistance of *Trichophyton mentagrophytes* arthrospores. *Appl Environ Microbiol.* 1978;25(2):274-277.
16. Bergman A, Casadevall A. Mammalian enothermy optimally restricts fungi and metabolic costs. *MBio.* 2010;1(5):e00212-10.
17. Bhanusali D, Coley M, Silverberg JI, Alexis A, Silverberg NB. Treatment outcomes for tinea capitis in a skin of color populations. *J Drugs Dermatol.* 2012;11(7):852.
18. Hainer BL. Dermatophyte infections. *Am Fam Physician.* 2003;67(1):101-109.
19. Habif TP. *Skin Diagnosis and Treatment.* 3rd ed. Philadelphia, Elsevier;2011:265-289.
20. Al Hasan M, Fitzgerald SM, Saoudian M, Krishnaswamy G. Dermatology for the practicing allergist: tinea pedis and its complications. *Clin Mol Allergy.* 2004;2(5):1-11.
21. Andrews MD, Burns M. Common tinea infections in children. *Am Fam Physician.* 2008;77(10):1415-1420.

Suggested Readings

- Dehghan M, Akbari N, Alborzi N, et al. Single-dose oral fluconazole versus topical clotrimazole in patients with tinea versicolor: a double-blind randomized controlled trial. *J Dermatol.* 2010;37(8):699-702.
- Delescluse J. Itraconazole in tinea versicolor: a review. *J Am Acad Dermatol.* 1990;23:551-554.
- Farschian M, Yaghoobi R, Samadi K. Fluconazole versus ketoconazole in the treatment of tinea versicolor. *J Dermatol Treat.* 2002;13(2):73-76.
- Ghannoum MA, Wraith LA, Cai B, Nyirady J, Isham N. Susceptibility of dermatophyte isolates obtained from a large worldwide terbinafine tinea capitis clinical trial. *Br J Dermatol.* 2008;159:711-713. doi:10.1111/j.1365-2133.2008.08648.x.
- Gupta A, Simpson F. Device-based therapies for onychomycosis treatment. *Skin Therapy Lett.* 2012;17(9):4-9.

- Gupta AK, Simpson FC. New therapeutic options for onychomycosis. *Expert Opin Pharmacother*. 2012;13(8):1131-42. doi: 10.1517/14656566.2012.681779 [Epub April 25, 2012].
- Hu SW, Bigby M. Pityriasis versicolor: a systematic review of interventions. *Arch Derm*. 2010;146(10):1132-1140.
- Kokturk A, Kaya TI, Ikizoglu G, et al. Efficacy of three short-term regimens of itraconazole in the treatment of pityriasis versicolor. *J Dermatol Treat*. 2002;13(4):185-187.
- Mendez-Tovar LJ. Pathogenesis of dermatophytosis and tinea versicolor. *Clin Dermatol*. 2010;28:185-189.
- Partap R, Kaur I, Chakrabarti A, et al. Single-dose fluconazole versus itraconazole in pityriasis versicolor. *Dermatology*. 2004;208(1):55-59.

I. BACKGROUND Granuloma annulare (GA) is a benign, typically self-limited, cutaneous disorder that is classically described as papules coalescing into annular plaques. There is a female predominance of 2.5:1, and the majority of patients are first affected prior to age 30. Localized GA is the most common clinical presentation, though clinical variations include generalized, subcutaneous, patch, and perforating forms. The most well-accepted hypothesis regarding pathogenesis involves a delayed-type hypersensitivity reaction. Other postulated mechanisms include vasculitis, trauma, and lysosomal enzyme release from monocytes induced by sensitized lymphocytes. Reported triggers include tuberculin skin tests, insect bites, sun exposure, and viral infections. GA has occurred in siblings and twins, and generalized GA has been associated with HLA Bw35, suggesting a genetic link. Lymphoma, solid organ malignancy, and leukemia have been reported in older patients with atypical GA lesions, but no definitive correlation exists. Similarly, the relationship between GA and diabetes mellitus has been debated for decades, and data remain inconclusive. A recent case-controlled study revealed a higher prevalence of dyslipidemia in GA patients, especially those with generalized GA.

II. CLINICAL PRESENTATION The lesions of GA are asymptomatic or mildly pruritic and most commonly present on the extremities, occasionally on the trunk, and rarely on the face. The subtypes differ in morphology, distribution, and age of those affected. While lesions may remit, reoccurrence is not uncommon (Table 17-1).

Localized GA is the most common subtype and presents as flesh-colored, arciform, or annular plaques on the extremities in limited quantity (Fig. 17-1). Plaque diameter ranges, and some lesions can measure upward of 5 cm. The age of onset is usually prior to 30, but localized GA can occur in older individuals. Approximately half of cases self-resolve; however, resolution can take years and recurrence at the same anatomic sites is common.

Generalized GA occurs in approximately 15% of GA patients, presents in a disseminated fashion on the trunk and extremities, and typically excludes mucous membranes, face, palms, and soles (Fig. 17-2). The lesions vary in color (skin-toned, red, tan, or yellow) and morphology (patches and papules) and can present as individual lesions or form reticulate or circinate patterns. Unlike the localized form, the age of onset for generalized GA is bimodal—either younger than 10 years or older than 40 years, and spontaneous resolution is less likely.

Perforating GA, subcutaneous GA, and patch GA are more rare (Figs. 17-3 and 17-4). Perforating GA affects both children and young adults and presents on dorsal hands and fingers. Lesions are primarily papules with a pustular-like,

TABLE 17-1 Clinical Features of Various Types of Granuloma Annulare

GA Subtype	Morphology	Distribution
Localized	Arciform or annular plaques	Distal extremities
Generalized	Papules or patches	Trunk and extremities
Perforating	Umbilicated and keratotic papules	Dorsal hands and fingers
Subcutaneous	Deep-seated and superficial nodules	Hand, palms, feet, anterior tibia, scalp, and periocular region
Patch	Erythematous patches, \pm annular lesions	Trunk, extremities

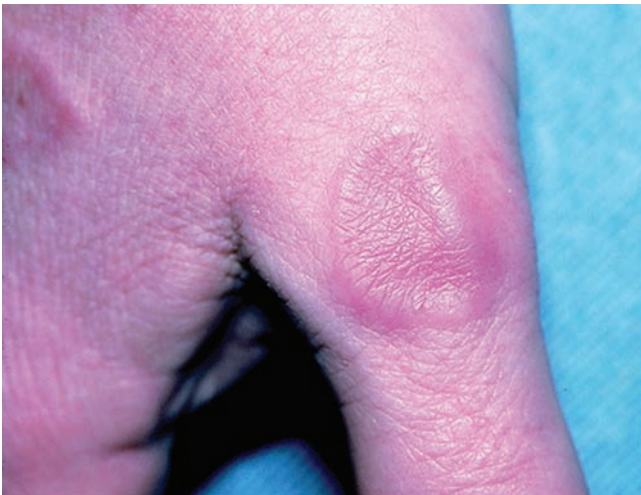


Figure 17-1. Localized granuloma annulare on the dorsal hand. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

umbilicated, or crusted component that may eventually develop into scars. Subcutaneous GA exists as deep-seated nodules or superficial papules on the hands, palms, feet, shins, and periocular region, more often in children than adults. Patch GA more commonly affects adults with red patches distributed on the trunk and extremities. Annular lesions may be seen.



Figure 17-2. Generalized granuloma annulare. (Reprinted with permission from Elsevier from Asano Y, Saito A, Idezuki T, Igarashi A. Generalized granuloma annulare treated with short-term administration of etretinate. *J Am Acad Dermatol.* 2006;54(5 Supl.):S245-S247.)



Figure 17-3. Perforating granuloma annulare. (Reprinted with permission from Elsevier from Kapembwa MS, Goolamali SK, Price A, Boyle S. Granuloma annulare masquerading as molluscum contagiosum-like eruption in an HIV-positive African woman. *J Am Acad Dermatol.* 2003;49 (2 Supl.):184-186.)



Figure 17-4. Patch granuloma annulare. (John H. Stroger, Jr. Hospital, Chicago, IL.)

III. WORKUP In unclear cases, histopathology is helpful. The mid and upper dermis exhibits degenerated collagen and deposition of mucin with surrounding palisades, or an interstitial pattern of histiocytes, lymphocytes, and fibroblasts. Mucin stains, such as colloidal iron and alcian blue, may be utilized (Table 17-2).

TABLE 17-2 Differential Diagnosis Based on Granuloma Annulare Subtype	
Granuloma Annulare Subtype	Differential Diagnosis
Localized/generalized/patch	Necrobiosis lipoidica diabetorum, annular sarcoidosis, annular elastolytic giant cell granuloma, erythema annular centrifugum, tinea corporis, secondary syphilis
Perforating	Molluscum contagiosum, perforating collagenosis, perforating folliculitis, pityriasis lichenoides et varioliformis acuta, flat warts, keratoacanthoma
Subcutaneous	Rheumatoid nodules, xanthomas, panniculitis, amyloid deposits, lymphomas, epidermoid inclusion cyst

TABLE 17-3	Treatment for Granuloma Annulare
Topical or intralesional corticosteroids	
Hydroxychloroquine, nicotinamide, and ofloxacin/rifampin/minocycline	
Isotretinoin and PUVA	

IV. TREATMENT Because GA is generally self-limiting and often remits spontaneously, patients may benefit from reassurance and clinical monitoring alone (Table 17-3). The recurring nature and cosmetic impact of the disease, however, can be distressing, and therapy should be tailored to the clinical picture and the patient’s treatment goals. First-line treatments for mild GA include high-potency topical steroids and intralesional steroids. Cryotherapy has been reported as a successful modality, but the risks of postprocedure scarring and atrophy should be weighed.

For extensive or recalcitrant GA, anecdotal reports have described various treatment regimens with variable success, although the self-resolving and recurring nature of the disease can make interpretation of the results difficult. Therapeutic options showing encouraging results include, but are not limited to, chloroquine, niacinamide, isotretinoin, psoralen and ultraviolet-A (PUVA), and a combination of rifampin/ofloxacin/minocycline. While reports of niacinamide are limited, one patient achieved clearance after 6 months of treatment at a dosage of 1,500 mg daily. The benefits of isotretinoin have been reported in several case reports, including cases of recalcitrant GA, with doses of 0.5 to 1 mg/kg. Given the significant side-effect profile of isotretinoin, careful monitoring is required. With PUVA therapy, clearance and improvement of lesions were noted in a few cases. Notably, the combination of monthly rifampin 600 mg, ofloxacin 400 mg, and minocycline hydrochloride 100 mg was used to treat six patients with recalcitrant generalized GA, and complete resolution occurred after 3 to 5 months. Interestingly, this regimen had been used to treat paucibacillary leprosy, which shares histopathologic findings with GA. Since biologic and immunosuppressant agents carry significant side-effect profiles, larger studies are needed to better assess their clinical utility in the treatment of GA.

Suggested Readings

Browne F, Turner D, Goulden V. Psoralen and ultraviolet A in the treatment of granuloma annulare. *Photodermatol Photoimmunol Photomed*. 2011;27(2):81-84.

Li A, Hogan DJ, Sanusi ID, Smoller BR. Granuloma annulare and malignant neoplasms. *Am J Dermatopathol*. 2003;25(2):113-116.

Looney M, Smith KM. Isotretinoin in the treatment of granuloma annulare. *Ann Pharmacother*. 2004;38(3):494-497.

Ma A, Medenica M. Response of generalized granuloma annulare to high-dose niacinamide. *Arch Dermatol*. 1983;119(10):836-839.

- Marcus DV, Mahmoud BH, Hamzavi IH. Granuloma annulare treated with rifampin, ofloxacin and minocycline combination therapy. *Arch Dermatol*. 2009;145(7):787-789.
- Muhlbauer JE. Granuloma annulare. *J Am Acad Dermatol*. 1980;3(3):217-230.
- Penas PF, Jones-Caballero M, Fraga J, Sanchez-Perez J, Garcia-Diez A. Perforating granuloma annulare. *Int J Dermatol*. 1997;36(5):340-348.
- Reisenauer A, White PK, Korcheva V, White C Jr. Granuloma annulare. In: Bologna JL, Jorizzo JL, Rapini RP, eds. *Bologna Textbook of Dermatology*. 3rd ed. Spain: Mosby Elsevier Publishing; 2012:1563-1566.
- Smith MD, Downie JB, DiCostanzo D. Granuloma annulare. *Int J Dermatol*. 1997;36(5):326-333.
- Wu W, Robinson-Bostom L, Kokkotou E, Jung H, Kroumpouzos G. Dyslipidemia in granuloma annulare, a case-control study. *Arch Dermatol*. 2012; 148(10):1131-1136.

I. BACKGROUND Cutaneous herpes simplex infections take two distinct forms: (i) the painful and disabling primary infection of previously uninfected individuals and (ii) the common, bothersome, recurrent form colloquially known as cold sores or fever blisters. These infections are asymptomatic in up to 80% of patients. The mode of transmission is by close personal contact. The virus is inoculated either through mucous membranes or through small cracks in the skin. By 4 years of age, approximately 50% of the population has antibodies to herpes simplex virus (HSV), indicative of prior exposure. This percentage increases to 60% to 70% by age 14. Following primary infection, effective immunity develops in some individuals, but 20% to 45% will have recurrent disease, and 7% of the general population has at least two episodes of recurrent orolabial HSV per year.

Herpes simplex is a DNA virus infecting humans alone that has an almost universal distribution. There are two types of HSV: type 1, which is usually responsible for nongenital herpetic infections; and type 2, which is usually the agent involved in genital infections in both men and women. It is important to recognize that the herpes virus has three unique properties. It has the capacity to invade and replicate within the nervous tissue. The virus then remains latent within the neural tissue, most commonly the trigeminal ganglia for HSV-1 and the sacral ganglia for HSV-2. Lastly, the latent virus has the capacity to reactivate and replicate causing cutaneous disease. There are certain biologic differences between the two types. For example, HSV-2 genital infections recur more frequently than HSV-1 genital herpes. However, nongenital HSV-1 infections recur more frequently than nongenital herpes due to HSV-2. Genital HSV infections recur sixfold more frequently than orolabial HSV infections. Previous infection with one type of HSV does not appear to provide effective immunity to subsequent infection with the other.

True primary infection occurs in a person with no previous exposure to HSV and is usually quite severe. First-episode genital infections can occur in persons who either had previous nongenital HSV infection or have serologic evidence of prior subclinical exposure to the virus. Although not sufficient to prevent reinfection, this degree of immunity at least confers partial protection such that first-episode genital infection is less severe than a true primary one. The primary infection has an incubation period of 3 to 12 days following exposure and runs a clinical course of 1 to 3 weeks. Viral excretion persists for 15 to 42 days after the primary infection. Recurrent lesions heal more quickly (7 to 10 days), and in recurrent orofacial disease most lesions are no longer excreting virus by 5 days. In women with recurrent genital herpes, virus is present for a mean of 4.8 days, while 16% may continue to shed virus from lesions

after 6 days. Asymptomatic shedding of HSV has also been demonstrated from both oropharyngeal and genital sites at low rates without evident lesions. The most recent studies suggest that transmission of genital herpes occurs most frequently from persons who asymptotically shed virus. The annual risk of transmission from a sexual partner with genital herpes in a heterosexual relationship is approximately 10%.

Genital herpes simplex is one of the most common sexually transmitted diseases (STDs). The prevalence of HSV-2 infection in the United States has been estimated to range from 20% to 60%. Even without considering its significant psychosocial impact, genital herpes simplex infection may pose other health problems for female patients. Pregnant women with a history of genital herpes must be carefully monitored. Women who have active, recurrent genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation, whereas Cesarean delivery is indicated in women with active genital lesions or prodromal symptoms (e.g., vulvar pain and burning) at the time of delivery.¹ The risk of HSV infection in neonates exposed to the virus at the time of vaginal delivery to mothers with a history of recurrent genital HSV infections is very low ($\leq 8\%$). The presence and titer of neutralizing antibody to HSV contribute to this low rate. In contrast, infants born to women with a primary HSV infection have a more than 50% risk of developing a clinical infection; Cesarean delivery is indicated. Neonatal herpes simplex infection is a serious disease with up to a 50% mortality rate and a significant chance of permanent sequelae among its survivors. Up to 60% to 80% of babies infected with HSV are delivered by women with no evidence of clinical HSV on examination. Disease during early pregnancy may produce malformations that are clinically indistinguishable from those produced by cytomegalovirus. Anorectal herpes is being recognized with increased frequency. When caused by HSV-2, it is usually transmitted by anal intercourse. HSV-1 causes perianal infections in immunosuppressed patients, presumably by autoinoculation from orofacial lesions.

After primary infection, the virus appears to remain latent in sensory ganglia. In patients with recurrent herpes, the virus is periodically reactivated and conducted to the epidermis through peripheral nerve fibers. It then replicates in the skin, producing the recurrent herpetic lesion. Trigger factors include emotional stress, physical trauma (including genital trauma), sunburn, menses, fever, and systemic infections. The long-term natural history of recurrent nongenital herpes infection is not well characterized. The virus type influences the recurrence rate of genital herpes, as does gender, with men being at greater risk for recurrent disease. There is a great deal of variation in recurrence rates among individuals. Over time, most patients experience clinically significant reductions in disease severity. Rates of recurrence begin to decline by the second year after initial outbreaks.²

Patients with atopic dermatitis risk the development of generalized lesions (eczema herpeticum), regardless of whether their eczema is active. Diseases or drugs that interfere with host response, particularly with cell-mediated immunity, also predispose to widespread, slowly healing, and more destructive infections. Those patients with lymphoreticular malignancies or thymic defects and immunosuppressed transplant or acquired immunodeficiency syndrome (AIDS) are most prone to severe HSV infections.

II. CLINICAL PRESENTATION

A. Primary Symptomatic Oral or Genital Herpes Simplex Virus Infections.

Infections on mucosal surfaces are preceded by a day or two of local tenderness. The lesions are accompanied by severe pain and tender lymphadenopathy, often making it impossible for those with gingivostomatitis to eat or drink or patients with extensive genital involvement to walk or urinate. High fever and purulent malodorous secretions accompany oral and vaginal infections. Primary genital infection in men usually results in painful penile lesions. It may also cause urethritis with dysuria and discharge. Anorectal infection may be complicated by tenesmus, constipation, and urinary retention.

Acute herpetic gingivostomatitis is the most frequent manifestation of primary infection, usually seen in young children. It is usually abrupt at onset and is associated with a high fever, anorexia, and listlessness. This acute episode lasts from 5 days to 1 week. Vesicles, erosions, and maceration are seen over the entire buccal mucosa; this can involve the perioral skin because of contamination. Marked erythema and edema of the gingiva are typical. Submandibular adenopathy is usually present and is tender. Acute herpetic pharyngotonsillitis is usually seen in adults and is an oropharyngeal infection of HSV-1. Symptoms are usually a sore throat, fever, malaise, and headache. HSV-2 can be an etiologic agent; however, this usually involves orogenital contact.

Vulvovaginitis is seen most frequently in girls and young women. It consists of widespread vesicles, erosions, and edema in the vulva, labia, and surrounding skin. These areas become very edematous, erythematous, and extremely tender. A profuse vaginal discharge is present, and some women develop urinary retention. Bilateral tender inguinal adenopathy is usually present. Cervicitis is often asymptomatic but nevertheless important to recognize in pregnant women because of the associated risk of fetal infection and spontaneous abortion. Pregnant women who acquire genital herpes during the first 20 weeks of pregnancy have an increased risk of abortions, whereas the infants of those who acquire an infection after 20 weeks have an increased incidence of prematurity and birth defects. Urethritis in men is accompanied by a watery discharge and the occasional presence of vesicles around the urethral meatus. Anorectal herpes is characterized by the typical cutaneous lesions as well as rectal ulcerations. Extensive indolent lesions are not uncommon in patients with AIDS. In the United States, genital ulcers are most commonly caused by HSV-2. These ulcers may contain multiple pathogens, and the patient should be evaluated for coexisting STDs. Most of the episodes of primary genital herpes are asymptomatic and up to 80% have no history of symptomatic genital herpes.

Inoculation herpes is commonly found on the paronychia area (herpetic whitlow) (Fig. 18-1) of nurses and physicians, particularly those involved with mouth care, and may also be found on previously traumatized or burned skin. The lesions are characterized by the sudden appearance of vesicles and are accompanied by extreme local pain, sometimes a sterile lymphangitis, and rarely a systemic reaction. The first episode may last up to 28 days. Recurrent infections most often occur in adults with HSV-2 infection. Herpetic whitlow is often misdiagnosed as a bacterial paronychia and mistreated with incision and drainage of lesions, with subsequent implantation of the virus into the



Figure 18-1. Herpetic whitlow. (From Berg D, Worzala K. *Atlas of Adult Physical Diagnosis*. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)

incised tissue. Herpes gladiatorum occurs among wrestlers, secondary to contact with opponents with active herpes virus infection.

B. Recurrent Herpes Simplex Virus Infections. Recurrent infection is termed herpes labialis or recurrent genital herpes. Lesions are preceded by several hours of a burning or tingling sensation in 80% of patients. They are uncomfortable, but much less than the lesions of the primary infection. Virus is present in the lesion at the time of prodromal symptoms. Multiple small vesicles, clustered together, appear at the site of prodromal symptoms. The vesicles may arise from normal skin or from an area that has a slight erythematous blush. Vesicles are initially clear, then become cloudy and purulent, dry, and crusty, and heal within 7 to 10 days. The mature lesion consists of grouped vesicles and/or pustules on an erythematous, edematous base. The presence of a yellow or golden crust on older lesions indicates bacterial superinfection. Regional, often tender, adenopathy is almost always present. Lymphangitis and lymphadenitis may be seen, particularly with recurrent lesions of the hands. The most common sites for lesions are on the face (lips, perioral area, cheeks, and nose) (Fig. 18-2) and neck. The next most common location is the anogenital area and then the sacrum and buttocks. However, recurrent herpes can be seen anywhere on the skin.



Figure 18-2. Recurrent herpes simplex virus infection (herpes labialis). Lesions are evident on the vermillion border of the lip and beyond. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

It is uncommon for recurrent lesions to be located inside the oral cavity except in the immunocompromised host. Recurrent erythema multiforme is often associated with HSV infection and typically responds to antiviral prophylaxis.

1. Differential Diagnoses. The differential diagnosis of orolabial herpes includes impetigo, herpes zoster, herpangina, aphthous stomatitis, Stevens-Johnson syndrome, pharyngitis, oral candidiasis, and drug-induced mucositis. While the typical lesions of recurrent orolabial HSV consist of tense grouped vesicles, those of bullous impetigo are flaccid, surrounding a crust. With HSV mucosal lesions, the anterior portion of the mouth is favored, whereas in herpangina the posterior pharynx is more commonly involved. In contrast, aphthous ulcers typically present as a single lesion on the buccal mucosa without associated vesicles. Erythema multiforme commonly occurs secondary to HSV, while the mucosal lesions of Stevens-Johnson syndrome need to be distinguished from HSV. Common mucosal manifestations of Epstein-Barr virus-induced mononucleosis include hyperemia of the oropharynx, exudative tonsillitis, and petechiae of the hard and soft palate. Oral candidiasis can present in many forms, including angular cheilitis, with erythema, fissuring, and edema at the angles of the mouth, acute or chronic pseudomembranous candidiasis, with a white slough on the tongue overlying erythematous and sometimes bleeding mucosa, as well as erythematous or hyperplastic candidiasis.

The differential diagnosis of genital herpes includes trauma, syphilis, chancroid, lymphogranuloma venereum, and genital aphthae. In contrast to genital herpes, the syphilitic chancre usually presents as a single lesion that is neither painful nor recurrent. The lesions of chancroid often manifest as multiple tender ulcers with a yellow-gray exudate overlying a base of granulation tissue.

Initial infection with chancroid and lymphogranuloma present is followed by the development of tender inguinal lymphadenopathy. Genital aphthae are typically round to oval with a yellow base and red rim. As these conditions can be difficult to distinguish from herpetic lesions, diagnostic tests for HSV (Tzanck, polymerase chain reaction [PCR], culture, or direct fluorescent antigen [DFA]) can be helpful to confirm the diagnosis. It is also important to be aware that combined infections commonly occur, especially in immunocompromised hosts.

III. WORKUP Any doubt concerning the presence of a herpes simplex infection may be clarified by multiple diagnostic procedures. The gold standard for detection of HSV is viral culture, typically yielding positive results within 48 hours. Immunofluorescent or immunoperoxidase techniques can be used to differentiate HSV-1, HSV-2, and varicella zoster virus. For a more rapid diagnosis, a cytologic smear (Tzanck smear) of the vesicle looking for giant cells and inclusion bodies is easily and quickly done (Fig. 18-3). The smears are positive in approximately 75% of virus culture-positive recurrent facial herpes but in only approximately 40% of ulcerative genital lesions. It is important that the earliest vesicle be chosen, and cells from the base of the vesicle will afford the best opportunity to detect the virus. Lesions of herpes simplex, herpes zoster, and varicella will have an identical appearance on biopsy and tissue smear. DFA testing can yield a result in a few hours if appropriate resources are available. Cells are scraped from ulcer bases and stained with a direct fluorescent antibody, able to distinguish HSV-1 from HSV-2. Skin biopsy of a typical viral vesicle will reveal a characteristic picture: (i) intraepidermal lesion located in the mid-to-upper epidermis, (ii) ballooning degeneration of cells, (iii) acantholytic cells floating free, and (iv) large, multinucleated viral giant cells. Intranuclear inclusions may be seen in the giant cells as well as in other

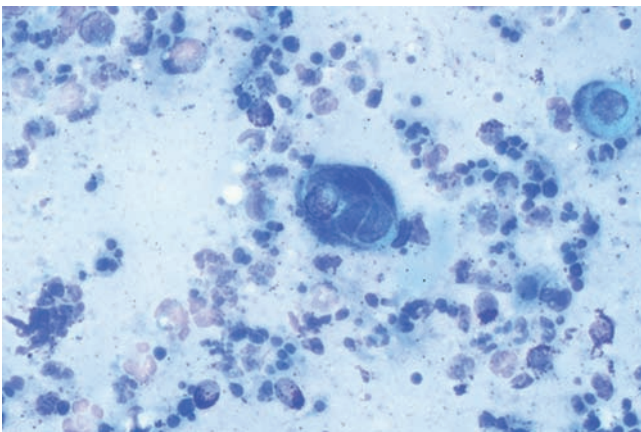


Figure 18-3. Tzanck preparation. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

infected epidermal cells. Specific neutralizing antibody titers will rise after the first week of primary infection and peak at 2 to 3 weeks, providing a useful test for seroconversions in childhood. PCR is a rapid and sensitive technique that is also available for use in certain clinical situations such as suspected HSV encephalitis.

IV. TREATMENT

A. Acyclovir. Acyclovir is a purine nucleoside analog that revolutionized the treatment of herpes simplex infections. Its safety and specificity are dependent on two factors: (i) a viral enzyme, thymidine kinase, is necessary for the conversion of the drug to its active form and (ii) once activated, acyclovir inhibits a virus-specific DNA polymerase required for viral replication (mammalian DNA polymerase is more substrate specific and therefore unaffected). Intravenous acyclovir (10 to 15 mg/kg IV q8h) is indicated mainly for the treatment of potentially catastrophic herpes infections in the normal (e.g., herpes encephalitis) or immunocompromised host. Treatment promptly aborts new lesion formation, reduces viral titers, promotes healing, and ameliorates pain. Intravenous acyclovir also effectively prevents reactivation of HSV in seropositive immunocompromised patients undergoing chemotherapy or transplantation. Eczema herpeticum and initial herpes infections in immunocompetent patients respond favorably as well. Oral acyclovir (200 mg po five times daily or 400 mg t.i.d. for 10 days) promotes resolution of primary and first-episode genital herpes infections if begun within 3 days of onset. Acyclovir treatment of the initial attack does not reduce recurrence rates. Patient-initiated early treatment (<48-hour duration) of recurrent genital herpes with acyclovir 800 mg t.i.d. or 200 mg five times a day for 5 days may shorten healing times and reduce the duration and formation of new lesions. If administered as a continuous dosage (400 mg b.i.d.) in patients who have frequent recurrences, acyclovir has been clearly shown to reduce or even prevent outbreaks. Because viral latency is unaffected by therapy, on discontinuation of such “prophylaxis,” recurrent attacks can be expected to resume as before treatment. Except for transient renal dysfunction if the intravenous form is administered too rapidly, acyclovir is remarkably free of side effects. The greatest concern is that with widespread use resistant viral strains will render this drug ineffective, especially in the treatment of the more serious infections. Resistance may occur through three mechanisms: (i) mutant viruses deficient in thymidine kinase, (ii) mutants with altered substrate specificity of thymidine kinase, or (iii) mutants with altered viral DNA polymerase enzymes.

B. Valacyclovir (Valtrex). Valacyclovir is a valine ester prodrug of acyclovir and has a bioavailability three to five times that of acyclovir, due to its improved gastrointestinal absorption compared with acyclovir. Valacyclovir is rapidly and almost completely converted to acyclovir after oral administration, with levels comparable to those of intravenous acyclovir. Valacyclovir is approved for herpes labialis, at 2,000 mg every 12 hours for 1 day at symptom onset. For primary genital herpes, valacyclovir is given at 1,000 mg every 12 hours for 10 days. For recurrent genital herpes, it is administered at 500 mg every 12 hours for 3 days at the onset of

prodromal symptoms or at the first sign of infection. This dosage regimen is as effective as five-times-daily acyclovir in the treatment of recurrent genital herpes in immunocompetent patients.³ Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome have occurred in patients with advanced human immunodeficiency virus disease, renal transplant, and bone marrow transplant. The most commonly reported adverse events are headache and nausea. Caution is advised in the use of valacyclovir in immunosuppressed and elderly patients. Dosing in immunocompetent patients can be seen in Table 18-1.

- C. Famciclovir (Famvir).** Famciclovir undergoes extensive first-pass metabolism to penciclovir after oral administration. Compared with oral acyclovir, famciclovir has improved bioavailability as well as a significantly prolonged intracellular half-life, allowing for less frequent dosing. Valacyclovir and famciclovir are similar in their high absorption, bioavailability, renal elimination, minimal drug interaction profiles, safety profiles, and efficacy. Oral famciclovir is indicated for recurrent orolabial herpes at 1,500 mg \times 1 dose. Famciclovir is administered for the treatment of primary genital

TABLE 18-1

Oral and Topical Medications for Herpes Simplex Infection in Immunocompetent Patients

Disease/ Etiologic Agent	Initial Disease	Recurrent Disease Episodic Disease	Suppressive Therapy
Herpes simplex labialis	Valacyclovir 1 g b.i.d. \times 10 d	Valacyclovir 2 g b.i.d. \times 1 d	Valacyclovir 500 mg q.d.
	Acyclovir 400 mg t.i.d. \times 10 d	Famciclovir 1,500 mg q.d. \times 1 d	Acyclovir 400 mg b.i.d.
		Acyclovir 400 mg t.i.d. \times 5 d	
		Topical 1% penciclovir q2h \times 4 d	
Herpes simplex genitalis	Valacyclovir 1 g b.i.d. \times 10 d	Valacyclovir 500 mg b.i.d. \times 3 d	Famciclovir 250 mg b.i.d.
	Famciclovir 250 mg t.i.d. \times 10 d	Famciclovir 1,000 mg b.i.d. \times 1 d	Valacyclovir 500 mg q.d. (if <10 episodes/y)
	Acyclovir 400 mg t.i.d. \times 10 d	Acyclovir 800 mg t.i.d. \times 5 d	Valacyclovir 1,000 mg q.d. (if 10 or more episodes/y)
			Acyclovir 400 mg b.i.d.

HSV infections at 250 mg po t.i.d. for 7 to 10 days. For recurrent genital herpes infections, famciclovir is administered at 1,000 mg twice daily for 1 day beginning at the onset of prodromal symptoms or at the first sign of infection. At recommended doses, treatment efficacy is similar to that with acyclovir.⁴ Oral famciclovir of 250 mg twice daily for up to 1 year is effective for the suppression of genital HSV infection.

- D. Foscarnet (Foscavir).** Foscarnet is approved by the U.S. Food and Drug Administration (FDA) for the treatment of acyclovir-resistant HSV infections in immunocompromised patients, a growing problem in the AIDS population. Foscarnet does not require HSV-encoded thymidine kinase, instead foscarnet reversibly binds near the pyrophosphate-binding site of DNA polymerase, halting DNA chain elongation. Foscarnet selectively inhibits viral DNA polymerase.⁵ Foscarnet therapy reduces the healing time, pain, and viral shedding. It is administered intravenously, 40 mg/kg every 8 to 12 hours for 14 to 21 days or until healed in patients with acyclovir-resistant herpes simplex infection. Associated side effects include azotemia secondary to nephrotoxicity, hyperphosphatemia, hypocalcemia, anemia, nausea, vomiting, and genital ulceration. Patients may eventually develop strains resistant to both acyclovir and foscarnet.
- E. Penciclovir (Denavir).** Penciclovir is another nucleoside analog that has a mechanism of action similar to that of acyclovir. Topical 1% penciclovir cream is indicated for the topical treatment of herpes labialis with application every 2 hours for 4 days. Topical penciclovir can reduce the time for healing of recurrent sunlight-induced herpes labialis by 2 days. Pain and discomfort are also diminished.⁶
- F. Docosanol (Abreva).** Docosanol 10% cream was approved by the FDA for over-the-counter topical use for recurrent herpes labialis with application five times per day for up to 10 days. In clinical trials, the use of docosanol decreased the healing time of herpes labialis by 0.7 days, which is similar to the modest benefit obtained with the use of topical penciclovir cream. Docosanol is commonly used as a filler in lipsticks and other cosmetics. Docosanol acts by inhibiting fusion between the human cell membrane and the HSV envelope, thereby preventing viral entry into cells and viral replication.
- G. General Measures.** The primary infection is extremely painful, and adequate analgesia is important. If salicylates or nonsteroidal anti-inflammatory drugs are inadequate, opiates may be needed for the first 7 to 10 days. When lesions are vesicular, apply cool compresses with tap water or Burow solution for 10 minutes t.i.d. to q.i.d. Cleansing mouthwashes [with benzalkonium chloride (Zephiran) 1:1,000 or tetracycline suspension 250 mg/60 mL H₂O] both clean and soothe the involved mucous membranes and decrease secondary bacterial superinfections. Vulvovaginitis and genital lesions may be aided by sitz baths in tepid water with or without Aveeno colloidal oatmeal. Women unable to void may sometimes be able to do so while in a bath. If not, intermittent catheterization or a temporary indwelling Foley catheter is necessary. Apply topical antibacterials such as mupirocin (Bactroban), povidone-iodine ointment, and bacitracin ointment to prevent bacterial superinfection.

Early and repeated application of a potent corticosteroid to recurrent lesions will often decrease its severity by inhibiting the inflammatory response. If this modality is used, the periorbital area must be avoided. If a consistent trigger factor for recurrent episodes can be identified, specific measures may be taken to counteract the stimulus (e.g., use of sunscreens). Treatment of primary infections is one of the few instances in which topical anesthetics are justified. Dyclonine hydrochloride (Dyclone), Benadryl elixir, or viscous Xylocaine may be used for oral lesions and benzocaine aerosol (Americaine) or Tronothane ointment may be beneficial symptomatically for the vulvar area. Application should be as frequent as necessary to keep the patient comfortable. The benzocaine preparations may sensitize the skin and should not be used routinely. Prophylactic systemic antivirals should be given before facial surgical procedures (chemical peels, laser surgery, dermabrasion, etc.) if the anatomic area involves the site of a previous HSV infection. Agents that have been shown to be ineffective or that have not been clearly shown to be useful include ethyl ether, chloroform, alcohol, idoxuridine, adenine arabinoside (Vira-A), vitamins C, E, and B₁₂, lactobacillus, 2-deoxy-d-glucose, zinc, lysine, povidone-iodine, dye-light (photodynamic inactivation), silver sulfadiazine (Silvadene), nonoxynol-9 cream, and dimethyl sulfoxide. Many HSV vaccines have been under investigation; however, most have not shown effectiveness in either the treatment or the prevention of herpes genitalis.

H. Ocular Infection. Patients with symptoms of corneal involvement (photophobia, pain) should be examined with a slit lamp. Herpes simplex keratitis is treated with trifluridine 1% ophthalmic solution (Viroptic), ganciclovir 0.15% ophthalmic gel (Zirgan), acyclovir, famciclovir, or valacyclovir. However, herpetic lesions of the lids and the immediate periorbital area, in the absence of ocular involvement, need not be treated with intraocular medication.

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REFERENCES

1. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. No. 82 June 2007. Management of herpes in pregnancy. *Obstet Gynecol.* 2007;109:1489-1498.
2. Benedetti JK, Zeh J, Corey L. Clinical reactivation of genital herpes simplex virus infection decreases in frequency over time. *Ann Intern Med.* 1999;131:14-20.
3. Tyring SK, Douglas JM Jr, Corey L, et al. A randomized, placebo-controlled comparison of oral valacyclovir and acyclovir in immunocompetent patients with recurrent genital herpes infections. The Valaciclovir International Study Group. *Arch Dermatol.* 1998;134:185-191.
4. Diaz-Mitoma F, Sibbald RG, Shafran SD, et al. Oral famciclovir for the suppression of recurrent genital herpes: a randomized controlled trial. Collaborative Famciclovir Genital Herpes Research Group. *JAMA.* 1998;280:887-892.

5. Wagstaff AJ, Bryson HM. Foscarnet. A reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with viral infections. *Drugs*. 1994;48:199-226.
6. Boon R, Goodman JJ, Martinez J, et al. Penciclovir cream for the treatment of sunlight-induced herpes simplex labialis: a randomized, double-blind, placebo-controlled trial. Penciclovir Cream Herpes Labialis Study Group. *Clin Ther*. 2000;22:76-90.

Suggested Reading

- Lin P, Torres G, Tyring SK. Changing paradigms in dermatology: antivirals in dermatology. *Clin Dermatol*. 2003;21:426-446.

I. BACKGROUND Infection with the varicella-zoster virus (VZV), a double-stranded deoxyribonucleic acid (DNA) virus, will produce one of two clinical entities. Generalized, highly contagious, and usually benign chickenpox represents primary infection in a nonimmune host, whereas localized and painful zoster, more commonly known as shingles, is recurrence of a latent infection in the partially immune host. Clinical manifestations reflect the interaction between the VZV and the host immune mechanisms.

Varicella infection, commonly known as chickenpox, is usually acquired through respiratory droplets. The disease is seen primarily in the winter and spring, has an incubation period of 10 to 23 days, begins abruptly, and lesions heal or even disappear within 7 to 10 days. Ninety percent of reported cases occur in children <10 years of age. Four percent of infections are subclinical. Almost every individual would have been infected by young adulthood. The disease is communicable from 1 day before the appearance of the exanthem to 6 days after; crusts are noninfectious. Signs, symptoms, and complications often become more severe with age; adolescents and adults may become severely ill, particularly with pulmonary involvement.

Primary VZV infections during pregnancy, although rare, can cause serious problems for both the mother and the child. The implications of primary infection vary significantly with the gestational age at infection. For the mother, the risk of severe illness is greatest after mid-pregnancy, when she is relatively immunocompromised. For the fetus, the risk of congenital infection is greatest when maternal infection occurs in the first or second trimester. Maternal infection is preventable by preconception vaccination.¹ Varicella pneumonia complicates up to 20% of cases of VZV infections in pregnancy. Symptoms usually appear about 4 days after the onset of the rash and may include cough, shortness of breath, chest pain, and hemoptysis. Congenital varicella syndrome, characterized by limb hypoplasia, muscular atrophy, skin scarring, cortical atrophy, microcephaly, cataract formation, and rudimentary digits, may also result from maternal varicella infection. The risks of these comorbid conditions are calculated to be 0.4% or 2% if infection occurs in the first 12 to 20 weeks.²

Zoster results from the reactivation of latent virus in dorsal root or cranial nerve ganglion cells. It is suspected that the virus is transported from the dorsal root or trigeminal ganglia through the myelinated nerves to the skin. As these nerves may terminate at the isthmus of hair follicles, primary infection first occurs in the follicular and sebaceous epithelium and then spreads to the rest of the epidermis. Histologic evidence reveals that zoster infection may occur exclusively in the folliculosebaceous units before the clinical appearance of vesicles.³

The incidence of zoster shows no seasonal variation. Two-thirds of patients are older than 40 years. Lesions erupt for several days and are usually

gone within 2 to 3 weeks in children and 2 to 4 weeks in adults. Zoster is a self-limited, localized disease that causes discomfort for several days but usually heals without complications. Postherpetic neuralgia (PHN) is seen with increasing frequency in those older than 60 years of age and can be extremely painful and sometimes chronic.

In patients with serious underlying conditions that alter immunologic competence, more severe disease develops. Lesions may be greater in number and persist for up to 7 months in the immunosuppressed; visceral dissemination can occur in 8% of untreated immunocompromised patients. For children with lymphoma or leukemia, varicella is a life-threatening infection; adults with such diseases often develop zoster, which may then disseminate. Dissemination occurs in only 2% to 4% of zoster cases in normal hosts. However, approximately two-thirds of patients with disseminated zoster have malignant disease. In patients known to be at risk for acquired immunodeficiency syndrome (AIDS), the occurrence of zoster may be one sign that heralds depression of cellular immunity and may be the first sign of human immunodeficiency virus (HIV) infection. HIV-infected patients may experience more severe primary infection or atypical varicella occurring concurrently with zoster.⁴

II. CLINICAL PRESENTATION

A. Varicella. Varicella in children is preceded by little or no prodrome; there may be only 24 hours of malaise and fever. In adolescents and adults, fever and constitutional symptoms almost always precede the exanthem by 24 to 48 hours. Patients are usually infectious for 1 to 2 days before the development of the rash and for 4 to 5 days following the beginning of the eruption, which is usually when the last vesicular crop has crusted. Patients often experience intense pruritus with the vesicular stage. The appearance of cough, dyspnea, and chest pain within 2 to 5 days after the onset of the rash is indicative of severe pulmonary involvement. Pruritus is the primary and most troublesome feature of chickenpox. Excoriation contributes to secondary bacterial infection and scarring.

Chickenpox begins abruptly with the appearance of discrete, erythematous macules and papules located primarily over the thorax, scalp, and mucous membranes; the face and distal extremities remain less involved (Fig. 19-1). Lesions progress rapidly from erythematous macules to 2 to 3 mm clear, tense, fragile vesicles surrounded by an erythematous areola. This appearance is often descriptively coined as “dew drops on a rose petal.” As the lesions progress, they first become umbilicated and then within hours become cloudy and purulent, with crusts forming in 2 to 4 days. Varicella lesions appear in 3 to 5 distinct crops for up to a 5-day period, and lesions in all stages of development may be seen within one area (Fig. 19-2). This is an important difference from smallpox. Crusts fall off in 1 to 3 weeks. Lesions usually heal without scarring. The most common complications are secondary bacterial infection of the skin lesions, usually staphylococci and streptococci. Adults often have a more complicated course with a more widespread rash, a prolonged fever, and an increased chance of complications, most commonly varicella pneumonia.

B. Herpes Zoster. The appearance of zoster lesions is frequently preceded by a mild-to-severe pre-eruptive pruritus, tenderness, or pain. The pain may be generalized over the entire nerve segment, localized to part of it, or referred.

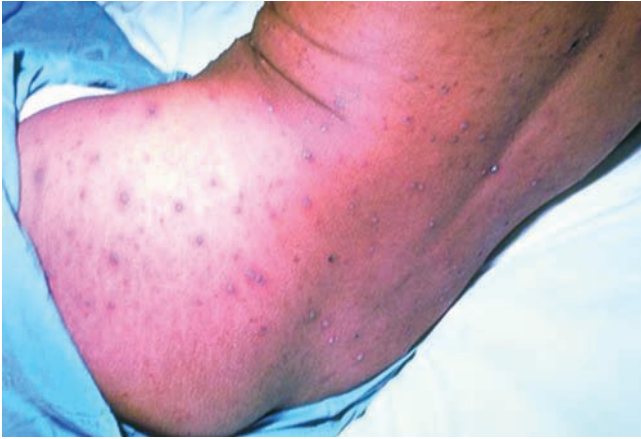


Figure 19-1. Varicella. (From Centers for Disease Control and Prevention Public Health Image Library.)



Figure 19-2. Varicella. Note the various stages of the lesions: papular, vesicular, and crusted lesions. (Courtesy of Shirley P. Klein, MD.)

Depending on the location, this pain may be confused with that of pleural or cardiac disease, cholecystitis or other abdominal catastrophe, renal or ureteral colic, sciatica, or other ailments. Neurologic changes within the affected dermatome include hyperesthesia, dysesthesia, and hypoesthesia. The interval between pain and eruption may be as long as 10 days but averages 3 to 5 days. In some patients, particularly children, there are no sensory changes. The pain will usually subside within several weeks, but 73% of patients older than 60 years of age have discomfort that persists beyond 8 weeks.

Zoster lesions first appear posteriorly and progress to the anterior and peripheral distribution of the nerve involved (see dermatome charts on the inside covers). Only rarely will the eruption be bilateral. Erythematous macules, papules, and plaques are seen first, and in most instances grouped vesicles appear within 24 hours, although occasionally blisters never develop. Plaques may be scattered irregularly along a dermatomal segment or may become confluent (Fig. 19-3). Mucous membranes within the dermatomes are also affected. The vesicles become purulent, crust, and fall off within 1 to 2 weeks. The presence of a few vesicles (10 to 25) outside the affected dermatome can occur and does not imply dissemination.

In >50% of individuals, zoster will involve the thoracic nerves; cervical or lumbar nerve involvement occurs in 15% to 20% of cases. Lesions on the tip of the nose herald involvement of the nasociliary branch of the ophthalmic division of the trigeminal nerve, implying a strong possibility of concomitant keratoconjunctivitis. Referral to an ophthalmologist for evaluation of ocular involvement is recommended. When herpes zoster occurs along the facial nerve and involves the geniculate ganglion—it may be accompanied by symptoms such as hearing loss and a rapid onset of facial pain. This combination of symptoms may indicate herpes zoster oticus, also called **Ramsay Hunt syndrome** (Fig. 19-4). On physical examination, there may be a unilateral herpetic rash of the pinna and peripheral facial paralysis. Patients may also experience a loss of taste and vertigo. Paresis and permanent motor damage are more common than previously thought and are found mostly with involvement of the trigeminal and upper cervical and thoracic nerves. Shingles may appear in multiple



Figure 19-3. Herpes zoster. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 19-4. Herpes zoster–Ramsey Hunt syndrome.

dermatomes both contiguous and noncontiguous and this is termed **zoster multiplex**,⁵ which is more common in immunocompromised individuals. VZV may reactivate without causing cutaneous vesicles but instead present with other symptoms and is termed **zoster sine herpette**. Overall incidence is 10% to 20%, with >66% of individuals affected with zoster being older than 50 years of age. Twenty-five percent of patients with HIV and 7% to 9% of patients with renal and cardiac transplant experience at least one episode of zoster. Ninety-five percent to 100% of individuals are seropositive for VZV antibodies. The disseminated form of zoster occurs in 2% to 20% of patients with herpes zoster, while up to 35% of patients with localized zoster will have a few scattered vesicles in remote sites. Those patients predisposed to more severe disease may show hemorrhagic, bullous, and infarctive-gangrenous lesions, which will heal slowly with scarring. Persistent varicella zoster in an immunocompromised host may present with atypical hyperkeratotic papules.

PHN is defined as pain persisting longer than 1 month up to at least 120 days following resolution of the vesicles. When the pain starts within 120 days of the rash, it is defined as subacute herpetic neuralgia. With acute infection there is direct viral damage and inflammatory neuritis of the peripheral nerve fibers, dorsal route ganglia, and the spinal cord. When the inflammatory phase decreases, fibrosis and destruction on nerve tissue begins and affects all levels of the pain pathway. PHN occurs in 9% to 14% of patients. Its incidence and severity are directly related to age. The incidence in patients between ages 30 and 50 is 4%, in contrast to 50% in patients over the age of 80. The pain improves from severe to mild in two-thirds of cases. Preexisting postherpetic pain is extremely difficult to alleviate. Researchers in the United Kingdom reported that after 3 months, 15% of patients still had pain and at 1 year roughly 5% to 10% still reported pain. Spontaneous resolution after 1 year is limited.⁶

C. Differential Diagnoses. The differential diagnoses of varicella includes herpes simplex virus (HSV), such as eczema herpeticum, other vesicular or bullous viral exanthems, drug eruptions, contact dermatitis, extensive

arthropod bites or scabies infestation, pityriasis lichenoides et varioliformis acuta, and, less commonly, rickettsialpox. Eczema herpeticum is a consideration in patients with a history of atopic dermatitis or other conditions that result in a compromised skin barrier. Disseminated HSV can mimic varicella closely. Viral exanthems such as those resulting from echovirus or cocksackievirus infection may also present with vesicular or bullous lesions, although lesions are typically located more distally on the extremities. Eczema vaccinatum and disseminated vaccinia are a possibility in those receiving vaccination for smallpox as well as their close contacts; and, although no longer naturally occurring, smallpox remains on the differential diagnoses. Rickettsialpox typically begins with a primary lesion that develops into an ulceration. Contact dermatitis is more likely to be localized and present on the extremities. Arthropod bites are usually localized, and the distribution of scabies lesions is distinct. In addition, secondary bacterial infection by *Staphylococcus aureus* or streptococcal species is the most common complication of varicella infection, so a positive bacterial culture does not exclude varicella.

The differential diagnoses of herpes zoster include HSV, localized bacterial infections such as bullous impetigo, contact dermatitis, and less commonly, other conditions such as trigeminal trophic syndrome. As opposed to the dermatomal distribution of herpes zoster, HSV and bullous impetigo are more likely to be localized centrally, crossing the midline, and more randomly distributed. Contact dermatitis is localized to the exposed area, which is usually different but may coincide with a dermatomal distribution. Trigeminal trophic syndrome presents with excoriations in a trigeminal distribution and usually spares the tip of the nose. In addition, disseminated zoster may occur in immunosuppressed patients, with a differential diagnoses similar to that of varicella described above.

III. WORKUP Infection may be confirmed by cytologic smear of the vesicle, viral culture, direct immunofluorescence with a monoclonal antibody, biopsy, or serologic methods (see Chapter 18, Workup section, for a more detailed description of these methods). In one study, of 56 patients with clinically typical herpes zoster, 64% had positive Tzanck smears, 55% had positive immunofluorescence assays, and 26% had positive cultures.⁷ Patients who are more at risk for severe varicella or those with disseminated zoster should be hospitalized and kept under strict precautions—in private rooms and away from seriously ill patients and those with lymphoproliferative disease or on immunosuppressive therapy. All patients with disseminated zoster or those severely ill with varicella should be investigated for underlying neoplastic or immunologic disease. Approximately 50% of adults with varicella show nodular pulmonary infiltrates, but not all will manifest clinical respiratory disease. A chest x-ray is indicated for evaluation. Nonimmune hospital employees who have been exposed to varicella should avoid patient contact for 8 to 21 days following exposure.

IV. TREATMENT

A. Varicella

- 1. Vaccination.** In March 1995, the U.S. Food and Drug Administration (FDA) approved the use of a live, attenuated varicella vaccine, Oka/

Merck strain (Varivax), for use in susceptible healthy children and adults. Prophylactic immunization for all children and adolescents susceptible to varicella is recommended. The current, 2012 American Academy of Pediatrics pediatric vaccination recommendations include an initial vaccination between 12 and 15 months, with a second dose between 4 and 6 years of age. For unvaccinated children, a two-dose regimen is also advised, with a minimum recommended interval of 3 months between 7 and 12 years of age and 4 weeks at 13 years or older.⁸ Long-term immunity of children having received the varicella Oka vaccine strain has been observed to persist 10 years after administration. The possibility of vaccine-induced primary varicella or herpes zoster infection is low. Vaccination of susceptible adults, particularly health-care workers, international travelers, day care workers, family contacts of immunocompromised patients, and nonpregnant women of childbearing age, should be performed. Adverse reactions to the vaccine include fever, infection-site reactions, and rash. The vaccine is contraindicated in patients with blood dyscrasias, patients with any malignant neoplasm of the bone marrow or lymphatic systems, patients on immunosuppressive therapy, patients with primary and acquired immunodeficiency states, active tuberculosis, or any febrile illness. Salicylates should be avoided for 6 weeks after vaccination to avoid Reye syndrome (Table 19-1).

2. **General Measures.** Most patients with varicella require only symptomatic therapy. Localized itching may be alleviated by application of a drying antipruritic lotion (calamine alone or with 0.25% menthol and/or 1.0% phenol). Lotions with phenol should not be given to pregnant women. Powdered oatmeal baths and antihistamines are also helpful for the pruritus. Salicylates should not be used for fever control to avoid Reye syndrome. The patient should cut nails short and keep hands clean, and children should wear gloves, if necessary, to prevent excoriation. Mouth and perineal lesions may be treated by rinses or compresses with 1.5% hydrogen peroxide, saline, or other agents. Apply topical antibiotic ointments to secondarily infected lesions. If infection is widespread, it is most often due to group A β -hemolytic *Streptococcus* or *Staphylococcus*, and systemic antibiotics should be used.
3. **Antiviral Therapy.** The American Academy of Pediatrics does not recommend oral acyclovir routinely for the treatment of uncomplicated varicella in otherwise healthy children. This is due to the marginal therapeutic effect, the cost of the drug, and the feasibility of drug administration in the first 24 hours. Acyclovir [20 mg/kg (not to exceed 800 mg) PO q.i.d. for 5 days] is indicated for children over 24 months with chronic cutaneous or pulmonary disorders, as well as adolescents, who are found to have more severe diseases than young children. If the child is over 40 kg, the adult dose is appropriate. Administration of oral acyclovir within 24 hours of onset for 5 to 7 days has been demonstrated to reduce the maximum number of lesions, shorten the time to healing, decrease the number of patients with fever by the second day, and decrease severe itching. Severe varicella, especially in the immunocompromised patient, should be treated with acyclovir as done for disseminated zoster. Antiviral treatment of varicella (800 mg PO q.i.d.

TABLE 19-1 Prevention and Treatment of Varicella Zoster Virus Infection

Disease/Etiologic Agent	Vaccination	Typical Treatment	Special Considerations
Varicella	Live, attenuated varicella vaccine—Oka/Merck strain (Varivax) Initial: 12–15 mo Second: 4–6 y	Children: Symptomatic therapy Adolescents and adults: Acyclovir 20 mg/kg (not to exceed 800 mg) q.i.d. × 5 d, start within 24 h of onset	Chronic cutaneous or pulmonary disorders: Acyclovir 20 mg/kg (not to exceed 800 mg) PO q.i.d. × 5 d Severe varicella, immunocompromised patients: Acyclovir 10 mg/kg IV q8 h × 7 d
Herpes zoster	Live, attenuated zoster vaccine—Oka/Merck strain (Zostavax) Single dose: 50 y of age and older	Acyclovir 800 mg 5×/day × 7–10 d Valacyclovir 1,000 mg t.i.d. × 7 d Famciclovir 500 mg t.i.d. × 7 d	Disseminated zoster, immunocompromised patients: Acyclovir 10 mg/kg IV q8 h × 7 d Acyclovir resistance: Foscarnet 40 mg/kg IV q8–12h × 10 d (only for acyclovir resistance)

for 5 days) in healthy adults, initiated the first day of illness, decreases the time of illness, decreases the time to healing, and lessens symptoms. Valacyclovir and famciclovir have not been extensively studied for use in primary varicella infection.

In the immunocompromised or immunosuppressed population, intravenous acyclovir therapy is recommended. This is generally done to decrease the likelihood of life-threatening complications associated with severe disseminated disease such as pneumonia, encephalitis, thrombocytopenia, and purpura. This population may also be complicated by acyclovir-resistant strains of VZV; foscarnet is a potential alternative therapy. The varicella-zoster immune globulin (VZIG) may be indicated in highly susceptible individuals. If given within 96 hours of exposure, the disease is not prevented but the course may be modified. VZIG is also indicated for infants born to mothers who experience the onset of chickenpox 5 days before delivery or within 2 days after delivery.

B. Zoster

1. **Vaccination.** The use of a live, attenuated zoster vaccine, Oka/Merck strain (Zostavax), to reduce the incidence of herpes zoster and PHN is FDA approved for individuals greater than 50 years of age. Studies have shown that VZV vaccines can significantly increase a person's cell-mediated immunity to VZV in immunocompetent older adults.⁹ The incidence of herpes zoster was reduced by 51.3% ($p < 0.001$), markedly reducing morbidity from herpes zoster and PHN among older adults.¹⁰ Zostavax is not indicated for the treatment of PHN. This live vaccine is contraindicated in immunosuppressed and pregnant patients.
2. **Acyclovir.** Acyclovir, a purine nucleoside analog, has been proven effective in both localized and disseminated zoster. Oral acyclovir (800 mg q4h, five times daily for 7 to 10 days), if started within the first 24 to 48 hours, is capable of shortening the time to lesion crusting, healing, and cessation of pain, and reducing new lesion formation. Treatment within 72 hours at onset may halve the incidence of residual neuropathic pain at 6 months in immunocompetent patients.¹¹ In the immunocompromised patient, acyclovir can also prevent or abort dissemination. Side effects are rare but include a transient recurrence of pain on discontinuing therapy and impaired renal function following rapid infusion. Acyclovir-resistant VZV infection has been reported in patients with AIDS. Valacyclovir and famciclovir are more bioavailable prodrugs of acyclovir.
3. **Valacyclovir.** Valacyclovir (Valtrex) is the L-valyl ester and prodrug of acyclovir. It displays improved bioavailability and prolonged half-life compared with acyclovir. The current recommended dose of valacyclovir is 1,000 mg by mouth three times a day for 7 days. Valacyclovir is superior in decreasing the duration of PHN and zoster-associated pain compared with acyclovir. A comparison study between valacyclovir and famciclovir showed no difference in effectiveness.¹² Caution is advised in the use of valacyclovir in immunocompromised patients. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome have occurred in patients with advanced HIV disease, renal transplant, or bone marrow transplant.

4. **Famciclovir.** Famciclovir (Famvir), another purine nucleoside analog, displays improved availability compared with acyclovir. The recommended dose is 500 mg three times a day for 7 days and the cost is similar to that of acyclovir. Famciclovir was effective in reducing PHN in individuals older than 50 years when compared with placebo. Valacyclovir and famciclovir appear to be equally efficacious for the treatment of herpes zoster and both may be superior to acyclovir in decreasing the duration of acute pain as well as PHN.
5. **Foscarnet.** Foscarnet is a pyrophosphate antagonist that inhibits DNA polymerase. It is approved for use in the treatment of acyclovir-resistant herpes zoster infections. It is administered intravenously, 40 mg/kg every 8 to 12 hours within 7 to 10 days in patients suspected of having acyclovir-resistant herpes zoster infection. Foscarnet is administered for 10 days. The associated side effects include azotemia secondary to nephrotoxicity, hyperphosphatemia, hypocalcemia, anemia, nausea, vomiting, and genital ulceration.
6. **General Measures.** Analgesics should be given as necessary. Opiates may be needed. For the vesicular stages, the following recommendations may also be effective.
 - Application of cool compresses with 1:20 Burow solution.
 - Painting of lesions with equal parts of tincture of benzoin and flexible collodion or with flexible collodion q12h.
 - Application of a drying lotion containing alcohol, menthol, and/or phenol.
 - Splinting the area with an occlusive dressing. Lesions should be covered with cotton and then wrapped with an elastic bandage as for a fractured rib.
 - When lesions are crusted and/or secondarily infected, Burow solution compresses should be applied and systemic antibiotics used if appropriate.
7. **Systemic Corticosteroids.** The use of systemic corticosteroids during acute zoster is controversial. When used appropriately in older individuals, corticosteroids decrease the severity of edema and pain and are very useful in patients with severe facial swelling either with or without ocular involvement. The risk–benefit ratio must be determined for each patient. Systemic corticosteroids should not be used in immunosuppressed patients or those with contraindications to corticosteroid use. Reduction in PHN by corticosteroids has not been demonstrated.¹³
8. **Ocular Involvement.** Ocular involvement of herpes zoster should be evaluated by an ophthalmologist. Herpes zoster keratoconjunctivitis is treated with topical ophthalmic corticosteroids. The distinction from herpes simplex keratitis is crucial, because the treatment is quite different (see Chapter 18, Treatment).
- C. **Post-herpetic Neuralgia.** While there are a large number of medications that are available for use in PHN, it remains difficult to treat as many have limited efficacy and/or problematic side effects that limit use in the elderly population most affected by PHN. The classes of medications most commonly used are tricyclic antidepressants, gabapentin and pregabalin, long-acting opiates, capsaicin, and topical local anesthetics.¹⁴

1. **Tricyclic Antidepressants.** The tricyclic antidepressants are well tested and effective for the management of PHN and are considered first-line agents for treatment. Amitriptyline (Elavil) is typically used with a starting dose of 10 to 25 mg nightly, increasing by 10 to 25 mg/day weekly up to a target of 75 to 150 mg nightly. The dose is then gradually tapered to discontinue. The use of amitriptyline has been demonstrated to reduce the prevalence of persisting pain at 6 months, so early treatment is optimal. Amitriptyline can be used in combination with either perphenazine (Trilafon) 4 mg t.i.d. to q.i.d., fluphenazine hydrochloride (Permitil) 1 mg t.i.d. to q.i.d., or thioridazine (Mellaril) 25 mg q.i.d. Nortriptyline (Aventyl, Pamelor) may be substituted for amitriptyline, with the former being as effective but associated with fewer unpleasant side effects.¹⁵ It may be necessary to continue medication for months. Before starting a tricyclic antidepressant, an electrocardiographic assessment for cardiac conduction abnormalities should be performed in patients over 40 years of age.
2. **Gabapentin (Neurontin) and Pregabalin (Lyrica).** Gabapentin and pregabalin significantly decrease pain scores and sleep interference associated with PHN. For gabapentin, an initial dose of 300 mg/day is increased over 4 weeks (900, 1,800, 2,400, and 3,600 mg/day divided t.i.d.) until efficacy is obtained or side effects become intolerable. Dose-limiting adverse effects include somnolence, dizziness, ataxia, peripheral edema, and infection. Pregabalin has improved absorption and more stable blood levels and is dosed at either 300 or 600 mg daily depending on renal function.
3. **Long-Acting Opiates.** Opioids are effective in controlling neuropathic pain. If required, long-acting agents should be chosen, and the duration of treatment should be limited with the patient subsequently transitioned to another class of agent. Importantly, constipation is a major side effect of opiate medications in the elderly, enhanced by decreased fluid uptake during painful zoster episodes. Bulk laxatives should be recommended during treatment.
4. **Capsaicin Cream (Zostrix).** Application of capsaicin cream 0.025% or 0.075% (Zostrix) t.i.d. to q.i.d. may cause pain relief in 25% and reduction of pain in as many as 80% of patients with PHN. Capsaicin, a derivative of hot chili peppers, depletes and prevents reaccumulation of the chemomediator substance P in peripheral sensory resources. However, the application of capsaicin itself may cause burning, which is intolerable in one-third of patients.
5. **Topical Local Anesthetics.** Local anesthetics, such as 10% lidocaine gel and topical 5% lidocaine–prilocaine cream (EMLA), may acutely reduce pain. A lidocaine 5% adhesive patch (Lidoderm) has been shown to significantly decrease acute pain in PHN compared with placebo with no systemic side effects.¹⁶ However, there does not appear to be any long-term benefit in reducing the prevalence of PHN.
6. **Other Options.** If a patient does not respond to any of the above therapeutic options, nonpharmacologic approaches may be considered and referral to a neurologist or pain-management specialist is recommended for further evaluation.

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REFERENCES

1. Gardella C, Brown ZA. Managing varicella zoster infection in pregnancy. *Cleve Clin J Med*. 2007;74:290-296.
2. Enders G, Miller E, Craddock-Watson J, et al. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. *Lancet*. 1994;343:1548-1551.
3. Walsh N, Boutilier R, Glasgow D, et al. Exclusive involvement of folliculosebaceous units by herpes: a reflection of early herpes zoster. *Am J Dermatopathol*. 2005;27:189-194.
4. Perronne C, Lazanas M, Lepout C, et al. Varicella in patients infected with the human immunodeficiency virus. *Arch Dermatol*. 1990;126:1033-1036.
5. Vu AQ, Radonich MA, Heald PW. Herpes zoster in seven disparate dermatomes (zoster multiplex): report of a case and review of the literature. *J Am Acad Dermatol*. 1999;40:868-869.
6. Bowsher D. The lifetime occurrence of Herpes zoster and prevalence of post-herpetic neuralgia: a retrospective survey in an elderly population. *Eur J Pain*. 1999;3:335-342.
7. Sadick NS, Swenson PD, Kaufman RL, et al. Comparison of detection of varicella-zoster virus by the Tzanck smear, direct immunofluorescence with a monoclonal antibody, and virus isolation. *J Am Acad Dermatol*. 1987;17:64-69.
8. Recommended childhood and adolescent immunization schedules—United States, 2012. *Pediatrics* 2012;129:385-386.
9. Levin MJ, Smith JG, Kaufhold RM, et al. Decline in varicella-zoster virus (VZV)-specific cell-mediated immunity with increasing age and boosting with a high-dose VZV vaccine. *J Infect Dis*. 2003;188:1336-1344.
10. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352:2271-2284.
11. Jackson JL, Gibbons R, Meyer G, et al. The effect of treating herpes zoster with oral acyclovir in preventing postherpetic neuralgia. A meta-analysis. *Arch Intern Med*. 1997;157:909-912.
12. Tyring SK, Beutner KR, Tucker BA, et al. Antiviral therapy for herpes zoster: randomized, controlled clinical trial of valacyclovir and famciclovir therapy in immunocompetent patients 50 years and older. *Arch Fam Med* 2000;9:863-869.
13. Whitley RJ, Weiss H, Gnann JW Jr, et al. Acyclovir with and without prednisone for the treatment of herpes zoster. A randomized, placebo-controlled trial. The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *Ann Intern Med*. 1996;125:376-383.
14. Tyring SK. Management of herpes zoster and postherpetic neuralgia. *J Am Acad Dermatol*. 2007;57:S136-S142.
15. Watson CP. A new treatment for postherpetic neuralgia. *N Engl J Med*. 2000;343:1563-1565.
16. Rowbotham MC, Davies PS, Verkempinck C, et al. Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. *Pain* 1996;65:39-44.

Suggested Reading

Lin P, Torres G, Tyring SK. Changing paradigms in dermatology: antivirals in dermatology. *Clin Dermatol*. 2003;21:426-446.

I. BACKGROUND Hidradenitis suppurativa (HS) is chronic, recurrent, scarring, inflammatory skin condition that involves the apocrine glands of intertriginous areas (Figs. 20-1 and 20-2). It has been estimated to affect 1% to 4% of the population. Most investigators do not report racial differences in incidence of this disease, but it has been established that women are more affected than men (3:1 ratio). The pathogenesis of HS remains unclear; however, follicular plugging, ductal rupture, and secondary inflammation are speculated to play a role. Additionally, genetic, mechanical, and hormonal processes are hypothesized to influence the disease.

II. CLINICAL PRESENTATION HS has a mean age of onset of 22 years, and the disease course lasts an average of 19 years. Patients present with tender, inflamed nodules, sinus tracts, and abscesses in intertriginous areas. Lesions may drain material that is serosanguinous, purulent, or a mixture of the two, and drainage may be malodorous. Clinical course of HS is variable, with some patients having an intermittent, mild chronic course, and others suffering from persistent, severe disease. Severity of HS is classified by Hurley stages (Table 20-1).

A thorough history and review of systems is important to determine the patient's genetic predisposition and risk for associated conditions. Approximately one-third of patients report a positive family history of HS, and families with autosomal dominant inheritance have been reported. Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome, Crohn disease, follicular occlusion tetrad, and pyoderma gangrenosum are all associated with HS (Table 20-2). In addition, there are rare reports of squamous cell carcinoma arising in chronic HS lesions.

HS often causes significant morbidity for patients. They may have difficulty with mobility due to pain, drainage from the lesions may require use of diapers, and the lesions often become intensely malodorous. These factors can cause the patient to become depressed, isolated, or even suicidal. It is important to screen for depression and talk to patients about their quality of life at regular intervals.

III. WORKUP The diagnosis of HS is usually made on clinical findings alone. However, a short list of differential diagnosis should be considered (Table 20-3). The Second International HS Research Symposium created the following diagnostic criteria (all three criteria must be met):

1. Typical lesions—nodules, abscesses, draining sinus, and bridged scars
2. Location—axillae, groin, genitals, perineal, perianal, buttocks, and infra- and intermammary regions
3. Chronic course and recurrences

Workup for associated diseases should be done on a case-by-case basis.

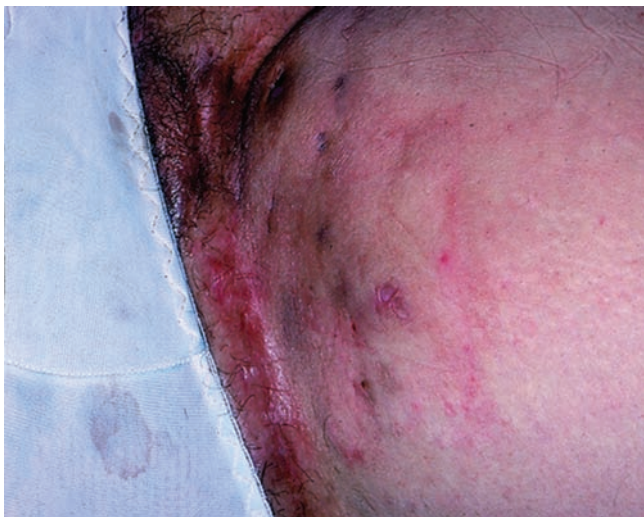


Figure 20-1. Hidradenitis suppurativa. This patient has involvement of the inguinal areas, labia majora, and medial thighs. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

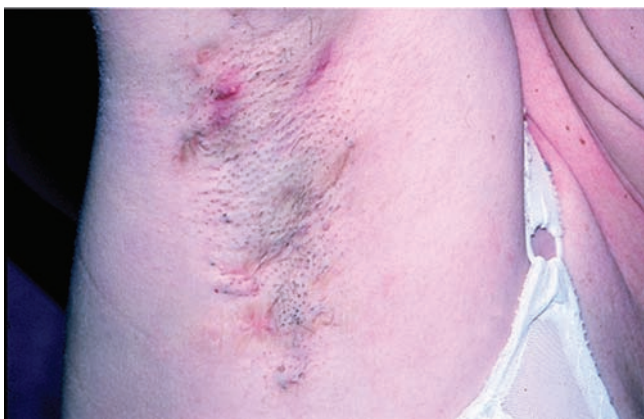


Figure 20-2. Chronic hidradenitis suppurativa. This patient has involvement of the axilla with bandlike hypertrophic scars. Note the characteristic paired open comedones and the single furuncle-like. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

TABLE 20-1 Hurley Stages

Stage I	Abscess formation, single or multiple without sinus tracts and scar
Stage II	Recurrent abscesses with tract formation and scar formation, single or multiple widely separated lesions
Stage III	Diffuse or near-diffuse involvement, or multiple interconnecting tracts and abscesses across entire area

TABLE 20-2 Diseases Associated with Hidradenitis Suppurativa

Follicular tetrad—follicular occlusive disease

- Acne vulgaris/conglobata
- Dissecting cellulitis
- Pilonidal cysts/sinuses

Rheumatologic diseases

- Arthritis
- Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome

Miscellaneous

- Crohn disease
- Pyoderma gangrenosum
- Dowling-Degos and Kitamura disease

TABLE 20-3 Differential Diagnosis of Hidradenitis Suppurativa

Infections	<ul style="list-style-type: none"> • Carbuncles, furuncles, and abscesses (including tuberculous) • Deep fungal infection • Sexually transmitted infections (granuloma inguinale, lymphogranuloma venereum, and noduloulcerative syphilis)
Tumors	<ul style="list-style-type: none"> • Cysts (epidermoid, Bartholin, and pilonidal)
Other	<ul style="list-style-type: none"> • Crohn disease • Anal or vulvovaginal fistulae

IV. TREATMENT HS is very difficult to treat, and there is often only partial response to therapy. Few randomized, controlled trials exist regarding HS treatments. Consequently, most treatment options are based upon case reports or case series. One strategy is to select the treatment appropriate for the severity based on Hurley stages (Table 20-4).

TABLE 20-4 Treatment Based on Hurley Stage

Stage I	Stage II	Stage III
1. Topical clindamycin 1% solution	1. Long-term tetracycline or dapsone for maintenance	1. Antibiotics
2. Antibiotics (7- to 10-d courses)	2. Clindamycin + rifampin for 3 mo if severe inflammation and little scarring	2. Corticosteroids (short-term relief for flares) and/or acitretin
• Tetracyclines		3. Surgery
• Amoxicillin-clavulanate		
• Clindamycin		
3. Intralesional triamcinolone	3. Intralesional triamcinolone	

A. Lifestyle Modifications

- 1. **Weight Loss.** Obesity results in more severe HS, possibly due to greater surface area of inverse skin, more friction in inverse areas, increased sweat retention, and increased serum proinflammatory cytokines. Weight loss should be a key discussion point with patients who have HS and obesity.
- 2. **Smoking Cessation.** There is a significant association between smoking and severe HS. Nicotine stimulates eccrine sweat glands, thereby causing plugging of glandular ducts, and leading to increased inflammation. Nicotine also stimulates chemotaxis of neutrophils, resulting in increased inflammation. Cigarette smoke itself upregulates expression of proinflammatory cytokines, such as interleukin-8 and tumor necrosis factor- α (TNF- α). Smoking cessation should be discussed with patients at each visit. Ideally, nicotine in any form should be restricted.
- 3. **Reduce Mechanical Friction and Trauma.** The following are techniques to help reduce follicular trauma and maceration:
 - Use hands, not a washcloth, to wash areas affected by HS
 - Wear loose fitting clothing (i.e., loose boxer shorts instead of tight undergarments)
 - Use tampons instead of sanitary napkins
 - Avoid manual manipulation (squeezing or pinching) of lesions

B. **Topical Washes.** Antiseptic washes—Washes such as chlorhexidine 4% are frequently prescribed to patients with HS in order to reduce bacterial colonization of the skin.

C. **Antibiotics.** Antibiotics are mainly used as anti-inflammatory agents in HS, rather than as antimicrobials. Bacteria are not thought to play a major direct role in HS, but may play a larger role in chronic, relapsing lesions of Hurley stage III HS. Although there are few randomized, controlled studies on the efficacy of antibiotics in the treatment of HS, they are still used extensively.

- Topical clindamycin 1% solution—A randomized placebo-controlled trial showed that twice daily use for 12 weeks reduced abscesses and pustules, but not inflammatory nodules. A 3-month study showed that a clindamycin solution was equally effective to using tetracycline 500 mg twice daily.

- Oral tetracyclines (doxycycline and minocycline)—These are commonly used as maintenance therapy in patients with chronic Hurley stage II HS.
- Oral clindamycin and rifampin—This regimen is usually used for 3 months in patients who have more inflammation and less scarring associated with their disease. Clindamycin and rifampin are both dosed at 300 mg twice daily.
- Dapsone and amoxicillin-clavulanate have also been used in the treatment of HS.

D. Corticosteroids. Both intralesional and systemic corticosteroids are used successfully in HS. Intralesional triamcinolone at doses of 5 to 10 mg/mL may resolve individual, acutely inflamed lesions. Higher doses of systemic corticosteroids can be used effectively to abort severe acute HS flares. Due to potential side effects of oral corticosteroid use, it is usually tapered over a short period.

E. Immunosuppressives. Immunosuppressive agents are typically reserved for patients with Hurley stage III severe HS.

- Cyclosporine—Three case reports have described rapid control of the disease with doses of 3 to 6 mg/kg.
- TNF- α inhibitors—TNF- α inhibitors as a possible treatment for HS were discovered surrendipitously when patients with HS receiving infliximab for Crohn disease were found to have improvement in symptoms of both diseases. Since that time, studies performed using etanercept, infliximab, and adalimumab for HS have yielded conflicting results. Although there is lack of strong evidence for their use, TNF- α inhibitors are still used off-label for treatment of severe HS.

F. Hormonal Therapy. Although the exact role of hormones in HS is unclear, the androgenic component of the disease is suggested by female predominance, premenstrual flares, and improvement during pregnancy. Anecdotal evidence of antiandrogen therapy with ethinylestradiol and cyproterone acetate has shown improvement in HS symptoms. Both medications bind to estrogen receptors and inhibit gonadotropin secretion. Cyproterone acetate is a partial androgen receptor agonist and has weak progestational activity.

G. Retinoids

Isotretinoin—While isotretinoin as a treatment for HS has been described in multiple studies, compelling data on its efficacy are limited.

Acitretin—In contrast to isotretinoin, acitretin has shown to be an effective treatment for HS. In a retrospective study of 12 patients with refractory HS treated with acitretin for 9 to 12 months, all achieved remission and experienced reduction of pain for a prolonged period. Acitretin can be used in men and in women of nonchildbearing potential.

H. Surgery

Incision and Drainage (I&D)—This is usually performed in acute settings when patients have painful, fluctuant abscesses. I&D can cause immediate relief of symptoms; however, lesions almost always recur, and it is not recommended for long-term control.

Deroofing—Deroofing may be performed in an attempt to spare tissue. The roof of the HS abscess or tract is removed, and the floor is left intact to heal by secondary intention.

Radical Wide Excision—There is observational evidence of a significantly lower rate of recurrence after wide excision of the entire hair-bearing affected region compared with limited local excision of only inflamed areas. Options for reconstruction after radical wide excision are primary closure, healing by secondary intent, split-thickness grafting, and fasciocutaneous or musculocutaneous flaps. Many surgeons prefer healing by secondary intention, due to low recurrence rates.

- I. Radiation Treatment.** External radiation beam therapy has been used with some success in recalcitrant cases of HS. This approach, however, is not commonly used, due to concern about long-term risks, including malignancy.
- J. Laser and Photodynamic Therapy.** Case series and reports have shown efficacy of various lasers for treatment of HS lesions. These include the 1,064-nm Nd:YAG laser, the carbon dioxide (CO₂) laser, and the 1,450-nm diode laser. Studies on the use of aminolevulinic acid photodynamic therapy (PDT) for HS have shown mixed results. There have been eight studies performed involving PDT, with only half of them showing some benefit.

Suggested Readings

- Boer J, Nazary M. Long term results of acitretin therapy for hidradenitis suppurativa. Is acne inversa also a misnomer? *Br J Dermatol*. 2011;164:170-175.
- Danby FW, Margesson LJ. Hidradenitis suppurativa. *Dermatol Clin*. 2010;28:779-793.
- Ellis, LZ. Hidradenitis suppurativa: surgical and other management techniques. *Dermatol Surg*. 2012;38:517-536.
- Jemec GBE. Hidradenitis suppurativa. *N Engl J Med*. 2012;366:158-164.
- Nazary M, Van der Zee HH, Prens EP, Folkerts G, Boer J. Pathogenesis and pharmacology of hidradenitis suppurativa. *Eur J Pharmacol*. 2011;672:1-8.
- Yazdanyar S, Jemec GBE. Hidradenitis suppurativa: a review of cause and treatment. *Curr Opin Infect Dis*. 2011;24:118-123.

I. BACKGROUND Hyperhidrosis is a condition of excessive sweating beyond the expected amount for environmental conditions and thermoregulatory needs. It can be a primary disease process, or it can occur secondary to medications or general medical conditions. Focal hyperhidrosis is a disorder of excess sweating usually in areas of high eccrine density, including the axillae, palms, soles, and, less commonly, the craniofacial area. Focal hyperhidrosis can be idiopathic, related to Frey syndrome (gustatory sweating), or related to neuropathies or spinal conditions. Generalized hyperhidrosis is characterized by diffuse sweating and can occur as the result of a myriad of underlying medical conditions, including endocrine, neurologic, malignancy, infection, cardiovascular, respiratory, medications, and toxicity.

Primary idiopathic focal hyperhidrosis, the form most often encountered in dermatology, has been estimated to affect 3% of the population. While the exact pathologic mechanism is unknown, it is thought that dysregulation of cholinergic fibers of the sympathetic nervous system plays an important role in its pathogenesis. Approximately two-thirds of patients with hyperhidrosis report a positive family history, suggesting a genetic basis for disease.

II. CLINICAL PRESENTATION Primary idiopathic focal hyperhidrosis affects men and women equally. The average age of onset is 25 years; however, palmar and axillary hyperhidroses exhibit earlier onset (Figs. 21-1 and 21-2). In order to diagnose primary focal idiopathic hyperhidrosis, the patient must have focal, visible, excessive sweating for at least 6 months with at least two of the following characteristics:

- Occurrence of at least one episode of sweating per week
- Sweating that is bilateral and relatively symmetric
- Impairment of quality of life/daily activities
- Onset before 25 years of age
- Positive family history of primary idiopathic focal hyperhidrosis
- Lack of sweating during sleep

It is important to keep in mind that hyperhidrosis may inflict a significant psychosocial burden on patients. It may cause social anxiety and embarrassment and impair daily activities and intimacy. Focal hyperhidrosis also predisposes patients for infection in the areas of excess perspiration, especially dermatophyte infections.

III. WORKUP It is important to distinguish between generalized and focal hyperhidrosis by taking a detailed history from the patient. When clinical presentation suggests idiopathic focal hyperhidrosis, no further workup is necessary. If there is suspicion of secondary or generalized hyperhidrosis, additional workup may be needed, including a detailed neurologic evaluation, blood



Figure 21-1. Palmar hyperhidrosis. (Courtesy of Julia Kasprzak, MD.)



Figure 21-2. Palmar hyperhidrosis. (Courtesy of Julia Kasprzak, MD.)

pressure reading, and laboratory tests (complete blood count, fasting serum glucose, and thyroid function tests).

The Hyperhidrosis Disease Severity Scale (HDSS) is a qualitative diagnostic tool that provides a measure of the impact on the patient's quality of life. This scale can help the clinician to tailor therapy to the severity of the case (Tables 21-1 and 21-2).

IV. TREATMENT Treatment options include nonsurgical (medical and procedural treatments) and surgical treatments (local dermatologic surgery for axillary hyperhidrosis and sympathectomy for refractory cases). Treatment is guided by severity of symptoms and, often, by the patient's insurance coverage. Topical medication is usually first-line therapy for focal idiopathic hyperhidrosis, due to its safety and efficacy profile. Procedural therapies such as botulinum toxin A (BTX-A) injections and iontophoresis are second-line treatments useful if topical or oral approaches are ineffective. Oral agents commonly used for hyperhidrosis include anticholinergics, antihypertensives, anxiolytics, and antidepressants; however, there are little data to support the use of oral medications (Table 21-3).

A. Aluminum Chloride Hexahydrate (AC). This is a well-established therapy for focal hyperhidrosis. AC blocks aluminum salt production in the distal acrosyringium, which leads to degeneration of the eccrine acini. Mild cases of hyperhidrosis may respond to over-the-counter antiperspirants. Unresponsive cases may demand prescription strength aluminum chloride 20% solution in ethanol. It should be applied nightly to the affected area, after it has been dried thoroughly. This can be done every night for 1 to 2 weeks, after which application frequency may be tapered. Irritation of the treated area, a common side effect, may be mitigated by occasional application of a low potency topical corticosteroid, such as hydrocortisone 1% cream, on the morning following treatment. A newer formulation of 15% aluminum chloride in salicylic acid gel appears to have similar efficacy as the standard formulation, with the benefit of decreased irritation.

B. Topical Glycopyrrolate. In patients with gustatory focal hyperhidrosis, topical application of 0.5% or 1% glycopyrrolate has been used successfully. In addition, in a small case series, 8 of 10 patients with postsympathectomy

TABLE 21-1 Hyperhidrosis Disease Severity Scale (HDSS)

Subjective	Score	Clinical Interpretation
Sweating is never noticeable and never interferes with daily activities	1	Mild
Sweating is tolerable but sometimes interferes with daily activities	2	Moderate
Sweating is barely tolerable and frequently interferes with daily activities	3	Severe
Sweating is intolerable and always interferes with daily activities	4	Severe

TABLE 21-2	Differential Diagnosis for Hyperhidrosis
Focal Hyperhidrosis Primary idiopathic hyperhidrosis Gustatory sweating Localized neuropathy or spinal injury	Generalized Hyperhidrosis Neurologic disease <ul style="list-style-type: none">• Stroke• Parkinson disease• Injury to spinal cord Endocrine abnormalities <ul style="list-style-type: none">• Hyperthyroidism• Hyperpituitarism• Diabetes• Pheochromocytoma• Carcinoid syndrome• Acromegaly Malignancy <ul style="list-style-type: none">• Myeloproliferative disease Respiratory failure Medications Infection Cardiovascular shock/heart failure Alcoholism/substance abuse

TABLE 21-3	Primary Treatment Options for Focal Hyperhidrosis (Axillary, Palmoplantar, and Craniofacial)
<ol style="list-style-type: none">1. Topical aluminum chloride2. Oral glycopyrrolate3. Botulinum toxin-A	

hyperhidrosis responded to a daily application of 2% glycopyrrolate. Glycopyrrolate blocks muscarinic receptors, thereby inhibiting cholinergic transmission. It is important to educate patients about potential anticholinergic side effects (visual changes, xerostomia, urinary hesitancy, tachycardia, dizziness, constipation, and confusion), although the risk with topical glycopyrrolate is lower compared with the oral formulation.

Physicians can work with their preferred compounding pharmacy to create 1% glycopyrrolate topical solution for patient use. There are also topical glycopyrrolate pads called Secure Pads®. They can be purchased from www.pharmacy.ca. Topical glycopyrrolate can be used every morning on affected areas and then washed off at night. If desired, the patient can apply topical aluminum chloride at night for additional benefit.

C. Iontophoresis. This treatment is best suited for palmoplantar hyperhidrosis. The introduction of an ionized substance through intact skin occurs by application of a direct current. Because sodium concentration and sweat volume decrease following treatment, it is thought that the mechanism of action involves changes in the resorption of sodium ions by the eccrine ducts. Patients place their hands or feet in plastic trays containing tap water

and electrodes. Initially, the treatment is performed every 2 to 3 days for 10 minutes a day. The energy is increased to reach the therapeutic range of 10 to 18 mA. After a therapeutic effect is achieved daily for 1 to 2 weeks, the treatment interval may be tapered. Home units are commercially available. Although pricing is variable, financial considerations must be discussed with patients as cost may be prohibitive. Common side effects include pain and irritation, which are generally proportional to amperage. Some studies have reported increased efficacy when BTX-A or glycopyrrolate were added to the iontophoresis solution.

D. Botulinum Toxin A. BTX is a neurotoxin that inhibits the presynaptic release of acetylcholine from postganglionic sympathetic nerve endings at the eccrine glands. It is Food and Drug Administration (FDA) approved for axillary hyperhidrosis and has been used off-label for palmo-plantar and craniofacial involvement.

Sweat reduction occurs in 82% to 87% of patients with axillary hyperhidrosis treated with BTX. The starch-iodine test is used in order to outline the hyperhidrotic area to be treated. This test first involves the application of 1% povidine-iodine solution to the clean, dry, shaved axillae. After the povidine air dries, a layer of corn starch is applied with cotton wool. When the patient starts to sweat, a blue-black precipitate forms, which outlines the area that needs injection with BTX (Fig. 21-3). Patients should stop all antihyperhidrotic therapeutic agents 5 days prior to iodine-starch testing. The area to be treated should be mapped with a marker; approximately 20 injections are needed for each axillae and should be spaced evenly 1 to 2 cm apart. Patients note a reduction in sweating 4 days to 2 weeks after the treatment. The duration of effect can range from 4 to 12 months.



Figure 21-3. Starch-iodine test. Blue-black streaks represent areas of increased sweating in the axilla. (Courtesy of Julia Kasprzak, MD.)

E. Oral Glycopyrrolate. The mechanism of action is the same as the topical formulation. This medication is considered second- or third-line therapy for severe focal hyperhidrosis involving the palmoplantar surfaces and/or axillae. Patients are usually given 1 to 2 mg once to twice daily. Anticholinergic side effects, as listed above under topical glycopyrrolate, are a common reason for discontinuation. Absolute contraindications to glycopyrrolate include myasthenia gravis, pyloric stenosis, and paralytic ileus. Caution should be taken when giving glycopyrrolate to those with gastroesophageal reflux disease, glaucoma, bladder outflow obstruction, and cardiac insufficiency.

A retrospective analysis was performed by Paller et al. (2012) of 31 children with palmoplantar or axillary hyperhidrosis who were treated with at least one dose of glycopyrrolate. They found that 90% of the patients reported overall improvement, with 70% reporting major improvement. Therapeutic effects dissipated within 1 day of discontinuation of the medication. The most common side effects reported included dry eyes and mouth; blurred vision and palpitations were reported in two isolated cases. Another retrospective study done by Walling (2012) sought to analyze the benefit of both clonidine and glycopyrrolate for palmoplantar, axillary, craniofacial, and generalized hyperhidrosis. A total of 67% of 45 patients experienced improvement with glycopyrrolate, while 47% of 13 patients improved with clonidine. Reported side effects of glycopyrrolate were similar to the Paller et al. study.

Of note, clonidine is an α -adrenergic receptor agonist that reduces sympathetic outflow. There have been limited case reports and series published about its use for the treatment of hyperhidrosis; therefore, it is not frequently used.

F. Surgery. Surgery is considered in severe cases refractory to medical treatments. Patients with recalcitrant axillary hyperhidrosis may undergo en bloc excision of axillary tissue to remove eccrine glands. This procedure is quoted to have relapse rate of only 10% to 25%; however, the cosmetic disfigurement and functional impairment of the area limit its use. Other less invasive surgical approaches to control axillary hyperhidrosis include curettage and liposuction.

Recalcitrant cases of focal hyperhidrosis may also be treated with video-assisted endoscopic thoracic sympathectomy. Greater than 95% of patients achieve long-term anhidrosis with this procedure. However, there are significant risks that range from life-threatening blood vessel or nerve injury to compensatory hyperhidrosis.

G. MiraDry®. MiraDry® is a new, noninvasive FDA-approved device that implements the use of microwaves to destroy eccrine glands at the dermal-hypodermal interface and provides a permanent decrease in sweating. A recent company-sponsored study written by Chih-HoHong et al. (2012) in *Dermatologic Surgery* showed that >90% of subjects ($n = 26$) had a decrease in their HDSS severity from 3 to 4 to a 1 or 2. Approximately 90% had a decrease in sweating greater than or equal to 50% of their baseline. Another finding included decreased odor associated with sweating. The most common side effects reported with the miraDry treatment were edema, erythema, and marks from the vacuum device. Some patients also reported some less common side effects including the following: altered sensation in the treated area, edema outside of the treated area, and transient neuropathy (one patient). All of these common and less common side effects had resolved during the study follow-up.

Suggested Readings

- Boni R. Generalized hyperhidrosis and its systemic treatment. *Curr Probl Dermatol*. 2002;30:44-47.
- Chih-Ho Hong H, Lupin M, O'Shaughnessy KF. Clinical evaluation of a microwave device for treating axillary hyperhidrosis. *Dermatol Surg*. 2012; 38:728-735.
- Flanagan KH, King R, Glaser DA. Botulinum toxin A versus topical 20% aluminum chloride for treatment of moderate to severe primary focal axillary hyperhidrosis. *J Drugs Dermatol*. 2008;7(3):221-227.
- Haider A, Solish N. Focal hyperhidrosis: diagnosis and treatment. *CMAJ*. 2005;172(1):69-75.
- Lowe NJ, Glaser DA, Eadie N, et al. Botulinum toxin type A in the treatment of primary axillary hyperhidrosis: a 52-week multicenter double-blind, randomized, placebo-controlled study of efficacy and safety. *J Am Acad Dermatol*. 2007;56:604-611.
- Paller AS, Shah PR, Silverio AM, et al. Oral glycopyrrolate as a second-line treatment for primary pediatric hyperhidrosis. *J Am Acad Dermatol*. 2012;67:918-923.
- Solish N, Bertucci V, Dansereau A, et al. A comprehensive approach to the recognition, diagnosis and severity-based treatment of focal hyperhidrosis: recommendations of the Canadian Hyperhidrosis Advisory Committee. *Dermatol Surg*. 2007;33:908-922.
- Walling HW. Primary hyperhidrosis increases the risk of cutaneous infection: a case-control study of 387 patients. *J Am Acad Dermatol*. 2009;61:242-246.
- Walling HW. Systemic therapy for primary hyperhidrosis: a retrospective study of 59 patients treated with glycopyrrolate or clonidine. *J Am Acad Dermatol*. 2012;66:387-392.
- Walling HW, Swick BL. Treatment options for hyperhidrosis. *Am J Clin Dermatol*. 2011;12(5):285-295.

I. BACKGROUND Hypertrichosis is defined as growth of hair on any part of the body in excess of the usual amount expected in a person of similar age, race, and sex.¹ Hypertrichosis should not be confused with hirsutism although the treatment options have significant overlap. Hirsutism is the androgen-dependent growth of hair in a male pattern in a female patient. Hypertrichosis is classified as generalized or localized and may be congenital or acquired. Several hair types may be involved, to include lanugo, vellus, and terminal hair. Hypertrichosis may be an isolated finding or may be associated with an underlying disorder.

Hair plays a significant role in social interaction. Hypertrichosis, if present, is often a stigmatizing factor. The presence of hypertrichosis is not only of cosmetic importance but may also be of medical importance, serving as a clue to internal pathology.

II. CLINICAL PRESENTATION

A. Generalized Hypertrichosis. Generalized hypertrichosis is the presence of increased lanugo, vellus, or terminal hair over a large portion of the body surface. Congenital hypertrichosis lanuginosa is an autosomal dominant disorder manifesting postnatally with diffuse growth of fine silver-gray to blonde lanugo hair which spares only the hands and feet. The lanugo hair may reach lengths greater than 10 cm. Acquired hypertrichosis lanuginosa is the sudden onset of rapidly growing fine lanugo hair over a large surface area. This rare form of generalized hypertrichosis has been reported to herald the presence of an underlying malignancy and has classically been associated with colorectal cancer but also described in association with many other malignancies. Another form of paraneoplastic hypertrichosis with a generalized presentation is POEMS (Polyneuropathy, organomegaly, edema, M-protein, skin abnormalities) syndrome which, in addition to hypertrichosis, presents with peripheral neuropathy, organomegaly, endocrine dysfunction, monoclonal gammopathy, and skin changes. Several drugs are known to cause generalized hypertrichosis (Table 22-1). Several congenital syndromes display generalized hypertrichosis and should be considered when evaluating an infant or young child with generalized hypertrichosis.

B. Localized Hypertrichosis. Localized hypertrichosis has both congenital and acquired forms (Figs. 22-1, 22-2, and 22-3). Becker nevus is a hamartoma, which exhibits hyperpigmentation and hypertrichosis (Fig. 22-4). It has a male predisposition and is typically first noticed in adolescence. Common locations include the shoulders and the upper lateral chest. Nevoid hypertrichosis is characterized as a circumscribed growth of terminal hairs within a patch of normally pigmented skin and without an underlying hamartoma.

TABLE 22-1 **Drug-Induced Hypertrichosis**

Cyclosporine
Diazoxide
Glucocorticosteroids
Interferon- α
Minoxidil
Penicillamine
Phenytoin
Prostaglandin analogs
Psoralens
Streptomycin
Zidovudine
EGFR inhibitors

EGFR, epidermal growth factor receptor.



Figure 22-1. Medium-sized congenital melanocytic nevus with hypertrichosis. (With permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 22-2. Hypertrichosis due to administration of intralesional corticosteroids. (Image provided by Stedman's.)



Figure 22-3. Steroid hypertrichosis. (Image provided by Stedman's.)

Inherited forms of hypertrichosis are often localized and frequently have a symmetric distribution (Table 22-2). Localized hypertrichosis following repeated trauma or friction is a well-known entity.

III. WORKUP Diagnosis of hypertrichosis is dependent on physical examination with characterization of the hair type involved, pattern of hair growth, and age of initial presentation. In addition, physical examination should focus on



Figure 22-4. Becker nevus. Note the hypertrichotic terminal hair growth over a hyperpigmented base.

TABLE 22-2 **Inherited forms of hypertrichosis**

	Onset
Becker nevus	First to second decade
Congenital melanocytic nevus	Early childhood
Plexiform neurofibroma	Childhood
Spinal dysraphism	Birth
Nevoid hypertrichosis	Birth to early childhood
Anterior cervical hypertrichosis	Birth to early childhood
Posterior cervical hypertrichosis	Birth
Hypertrichosis cubiti	Birth to early childhood
Hairy palms and soles	Birth
Hypertrichosis of the auricle	First to second decade
Hypertrichosis of the nasal tip	Adolescence

any associated abnormalities, which may signal the presence of an underlying disorder. Family history and medication history are helpful with diagnosis as well. Biopsy has limited utility in the diagnosis of hypertrichosis. A female patient with hirsutism should be screened for an ovarian or adrenal source of androgen production.

IV. TREATMENT Treatment options vary greatly in duration of effect, convenience, effectiveness, associated discomfort, and cost to the patient. Treatment must be individualized to each patient as one form of treatment may not be acceptable to a patient with generalized disease that is a viable option for a patient with localized disease. Patient expectations must be addressed prior to treatment and, in particular, duration of treatment discussed. Long-lasting hair eradication may be possible in some patients but no single method of treatment has been demonstrated to provide permanent, complete hair removal in all patients (Table 22-3).

- A. Shaving.** Shaving has long been a popular method of hair removal for men and women alike. Shaving is quick, accessible, effective, and affordable. Contrary to popular belief, shaving does not increase the rate of hair growth or the width of hair that has been shaved. However, the hair that resurfaces is not finely tapered and gives the appearance of being coarse.¹ This results in the need to shave frequently. Shaving is often perceived as an unacceptable treatment for excess hair growth on the face of women.
- B. Tweezing.** Tweezing or plucking is a useful method of epilation. Advantages of tweezing include ready accessibility, low cost, and ability to easily localize treatment. Disadvantages of tweezing are that it is uncomfortable, time-consuming, temporary, and may lead to folliculitis, hyperpigmentation, ingrown hairs, or follicular distortion. Tweezing is most useful for epilation of small treatment areas.
- C. Waxing.** Waxing is one of the most commonly used methods of physical epilation. Waxing involves applying a thin layer of soft wax to the treatment area. The wax then hardens around the hair shaft and as the wax is peeled from the skin the hair is removed from the hair bulb. Waxing provides a longer lasting effect, approximately 2 to 6 weeks, than either shaving or chemical depilation. Waxing is a relatively inexpensive method of epilation and easily accessible. Risks of treatment include skin irritation, folliculitis, contact dermatitis to allergic sensitizers in wax, and thermal burn from the application of hot wax.

TABLE 22-3	Treatment Options
<ol style="list-style-type: none">1. Shaving/tweezing/waxing2. Chemical depilatories3. Eflornithine cream (Vaniqa)4. Electrolysis and thermolysis5. Light and laser methods	

- D. Chemical Depilatories.** There are two general classes of chemical depilatories: sulfides of alkali metals and thioglycolate salts. Both achieve chemical depilation through the hydrolization of disulfide bonds within the hair shaft. Chemical depilatories break down the hair shaft at the level of the skin surface or at the level of the follicular infundibulum. Chemical depilatories do not remove the hair shaft from the hair bulb. Therefore, chemical depilation retreatment must be performed every week to 2 weeks for maintenance.
- E. Eflornithine 13.9% Cream (Vaniqa).** A newer method of treatment for hypertrichosis is topical treatment with eflornithine cream. Eflornithine hydrochloride works as an inhibitor of ornithine decarboxylase to slow the growth of hair through regulation of cell division. The cream is applied twice daily with results expected in 4 to 8 weeks. Eflornithine 13.9% cream has been approved for the treatment of facial hirsutism in women. One area where eflornithine has been found to be effective is in combination with light-based hair removal systems. Adverse effects have included local skin irritation and an acne-like eruption. Hair regrowth will occur with cessation of treatment with eflornithine.
- F. Electrolysis and Thermolysis.** Electrolysis is achieved by passing a current through tissue by means of a small needle inserted into a hair follicle. The current produces sodium hydroxide from water and sodium chloride and destroys the hair follicle leaving behind a microscar which is nearly imperceptible at the skin surface. Electrolysis requires the treatment of each individual hair follicle for a minute or longer and can be very time-consuming.

Thermolysis utilizes a high-frequency alternating current passed down the electrolysis needle or probe to destroy the hair bulb with heat. Thermolysis requires application to each follicle for only a few seconds to destroy the hair follicle. Thermolysis has a higher risk of scarring and pain than electrolysis but most newer devices have automated timers and insulated probes to minimize this risk.

Electrolysis and thermolysis may be used in combination through a single needle to produce an even more effective means of electrosurgical epilation. The use of this combination has been reported to be less painful than electrolysis and may be performed as rapidly as thermolysis.

Patients must be advised that treatment with electrolysis or thermolysis may cause significant discomfort during the procedure. Risks of electrosurgical epilation include transmission of infectious disease and risk is limited by the use of disposable electrolysis needles. Herpes simplex virus reactivation may also occur and prophylactic treatment with antivirals should be considered in areas of high risk such as the upper lip and chin. There is also a theoretical risk of cardiac pacemaker interference or dysfunction with electrosurgical techniques. In addition, patients prone to hypertrophic scarring, keloid formation, or postinflammatory hyperpigmentation should be advised that these complications are possible.

- G. Laser-Assisted Hair Removal.** Laser-assisted hair removal is an effective means to treat large areas of excess hair growth in a relatively timely and long-lasting or permanent manner with less discomfort than some other therapeutic options. The ultimate target for destruction is the stem cell residing in the bulge region of the hair follicle. Photoepilation is achieved

through selective photothermolysis, where a chromophore is targeted by an appropriate choice of wavelength, pulse duration, and fluence. Melanin is the targeted chromophore in laser-assisted hair removal and has an absorption spectrum of 400 to 1,200 nm. Lasers that operate in the red or near-infrared wavelength region are most effective. Wavelengths in the 600 to 1,100-nm range allow for deep penetration into the dermis and the melanin-containing hair shaft, hair follicle epithelium, and hair matrix. Lasers meeting this qualification include the 694-nm ruby, 755-nm alexandrite, 800-nm diode, and 1,064-nm Nd-YAG lasers.²

Achieving long-term hair removal with lasers is not as simple as choosing a device with a wavelength between 600 and 1,100 nm. Other factors must be taken into consideration and these include pulse duration and fluence. Pulse duration is chosen based on the thermal relaxation time of the hair follicle. If the pulse duration is too long, thermal damage will extend beyond the targeted structures of the hair follicle. If the pulse duration is too short, the nonpigmented structures, which may be at some distance from melanin-containing follicular components, will not be destroyed and long-term hair removal will not be achieved. Higher fluences are more effective in hair removal but must be tailored to patient skin type with avoidance of undesired effects.

A patient should be advised that 6 to 10 treatments may be necessary to achieve long-term efficacy with any laser system used. The treatments are generally spaced at 6- to 10-week intervals, with the exception that the beard region of men and women may be retreated at 3 to 4 weeks and the face at monthly intervals. Treatment efficacy varies based on skin type and hair color with the rule-of-thumb being patients with fair skin and darker hair will have a better response. A review of laser and light source hair removal controlled clinical trials estimated that after three to five repetitive treatments, a partial hair reduction of 50% at 1 year may be achieved.³

One potential complication of laser-assisted hair removal is thermal damage to the overlying melanin-containing epidermis. Removal of hair preoperatively by shaving is necessary to prevent conduction of the thermal energy from the exposed hair shaft to the surrounding epidermis. In addition, several methods of cooling the skin have been developed to assist in minimizing the thermal injury and these include the use of cryogen spray devices, application of contact cooling, and chilling the skin with cold air. Paradoxical hypertrichosis is a well-documented undesired effect in a small but significant percentage of patients receiving treatment with lasers as well as intense pulsed light (IPL). Paradoxical hypertrichosis has been associated with treatment with alexandrite laser, diode laser, and IPL but is likely to be common to all laser and light hair removal devices. The incidence of paradoxical hypertrichosis has been estimated at 0.6% to 10%.⁴

H. Intense Pulsed Light. IPL achieves hair removal by a means similar to laser treatments in that it is based on the principle of selective photothermolysis. Filters are placed on an intense, pulsed, nonlaser light source to produce a wavelength from 590 to 1,200 nm. Fluences in the range of 30 to 65 J/cm² are utilized. Cooling is achieved by contact cooling. Similar to treatment with lasers, patients with darker hair tend to achieve better results. Up to 87% hair reduction has been reported after 27.4 months and eight treatments.⁵

I. Photodynamic Therapy. At this time PDT is not commonly used for hair removal but remains a possible treatment option for the future. PDT

involves the topical application of aminolevulinic acid (ALA) followed by red light exposure. ALA promotes the production of protoporphyrin IX which is a potent photosensitizer. With exposure to red light, cell membrane damage is elicited within the hair follicle as a result of the creation of singlet oxygen. Prior to treatment with PDT, wax epilation is performed in the treatment region, which increases hair follicle exposure to the ALA. A potential advantage of PDT is that it theoretically would work equally as well on all skin and hair colors.

REFERENCES

1. Trueb RM. Causes and management of hypertrichosis. *Am J Clin Dermatol*. 2002;3(9):617-627.
2. Dierickx CC. Hair removal by lasers and intense pulsed light sources. *Semin Cutan Med Surg*. 2000;19(4):267-275.
3. Haedersdal M, Wulf HC. Evidence-based review of hair removal using lasers and light sources. *J Eur Acad Dermatol Venereol*. 2006;20(1):9-20.
4. Desai S, Mahmoud BH, Bhatia AC, Hamzavi IH. Paradoxical hypertrichosis after laser therapy: a review. *Dermatol Surg*. 2010;36(3):291-298.
5. Nouri K, Vejjabhinanta V, Patel SS, Singh A. Photoepilation: a growing trend in laser-assisted cosmetic dermatology. *J Cosmet Dermatol*. 2008;7:61-67.

Suggested Readings

- Liew SH. Unwanted body hair and its removal: a review. *Dermatol Surg*. 1999;25:431-439.
- Wanitphakdeedecha R, Alster TS. Physical means of treating unwanted hair. *Dermatol Ther*. 2008;21:392-401.
- Wendelin DS, Pope DN, Mallory SB. Hypertrichosis. *J Am Acad Dermatol*. 2003;48:161-182.

PEDICULOSIS

I. BACKGROUND Infestation with lice is known as pediculosis. There are two species of lice specific to the human host: *Phthirus pubis* (Fig. 23-1) and *Pediculus humanus* (Fig. 23-2). These wingless, six-legged insects are obligate parasites and are host specific for humans. The lice that inhabit the head or body are both types of *P. humanus* (*P. humanus humanus* and *P. humanus capitis*); only the body louse is capable of transmission of disease-endemic typhus (*Rickettsia prowazekii*), trench fever (*Bartonella quintana*), and relapsing fever (*Borrelia recurrentis* and *Borrelia duttoni*). *Pediculus capitis* is not known to be a disease vector. The head louse is transmitted through shared clothing and brushes; the body louse, by bedding or clothing; and the pubic louse, from person-to-person contact and not infrequently through clothing, bedding, or towels.

The adult body louse (*Pediculosis humanis*) is 2 to 4 mm long, has three pairs of legs with delicate hooks, and is gray-white in appearance. Body lice prefer to live in clothing, particularly seams, and move to the body to feed. Heavy infestation is common in crowded, unhygienic surroundings such as military personnel and refugees during wartime, prisons, chronic health-care institutions, and homelessness. Head lice (*P. capitis*) most commonly affect children, between the ages of 3 and 11. The incubation period from exposure to pruritus is approximately 30 days. The ova (nits), which are oval, 1 mm long and gray, and firmly attached to the hair, hatch in approximately 7 to 9 days and become mature in another week (Fig. 23-3). Ova are laid very close to the scalp and hatch before the hair grows more than 1/4". If no nits are found within 1/2" of the scalp and no lice are seen, treatment is not necessary because nits more than 1/2" from the scalp are eggshells from a past infection. Head lice do not jump or fly from one person to another.

The crab or pubic louse (*P. pubis*), which usually inhabits the genital region, is short (1 to 2 mm) and broad, and the first pair of legs is shorter than the claw-like second and third pairs. Infestation may occur in other areas, including the moustache, beard, axillae, chest, scalp, and eyelashes. Adult lice can live off the host for up to 36 hours and viable eggs, for 10 days. The chance of acquiring pediculosis pubis from one sexual exposure with an infected person is approximately 95%. Transmission of crab lice can occur without body contact, especially in warmer environments.

II. CLINICAL PRESENTATION Extreme pruritus is the primary characteristic of pediculosis. It takes 4 to 6 weeks for the pruritus to develop in a non-sensitized individual and only 24 to 48 hours with repeat exposures. Chronic infection may lead to lichenification and hyperpigmentation from repeated scratching. In some cases, patients may be totally asymptomatic. Sleeplessness

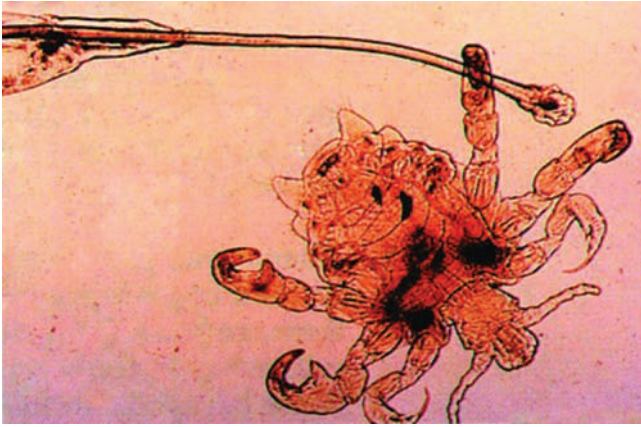


Figure 23-1. Pubic louse (crab). (Washington Winn Jr. *Koneman's Color Atlas and Textbook of Diagnostic Microbiology*. 5th ed. Philadelphia, PA: Lippincott-Raven; 1997.)

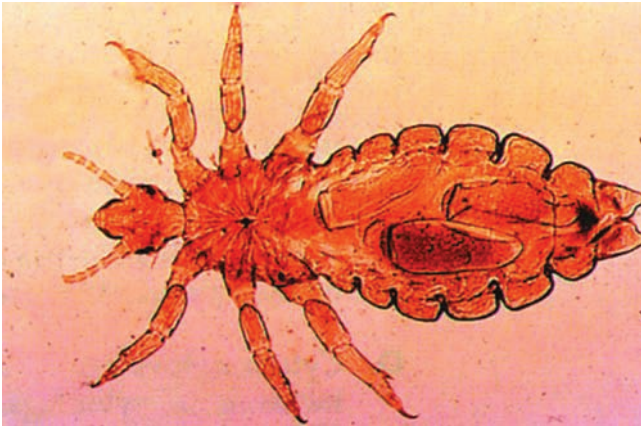


Figure 23-2. Body louse. (Washington Winn, Jr. *Koneman's Color Atlas and Textbook of Diagnostic Microbiology*. 5th ed. Philadelphia, PA: Lippincott-Raven; 1997.)

may be reported, because lice are more active during nocturnal hours. Nits may be found most easily on the hairs on the occiput and above the ears. It is often difficult to differentiate a viable from a nonviable nit. Pseudonits are desquamated epithelium encircling the hair but are more readily removed than true nits. Secondary impetigo and furunculosis with associated cervical lymphadenopathy may occur. In severe cases, fever and anemia may be found. Feeling “lousy” was a term developed to describe the symptoms of pediculosis.

In cases of body lice, scratch marks, eczematous changes, lichenification, urticaria, and persistent erythematous papules may be seen. Lesions are often

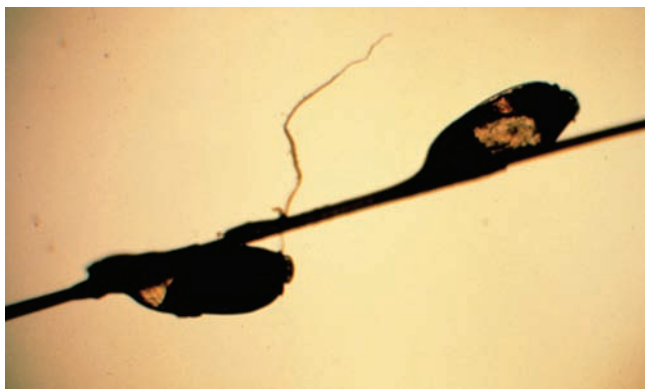


Figure 23-3. Nits. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

most noticeable on the back. The lice will be found in the seams of clothing and only rarely on the skin.

Unexplained pubic pruritus is very often a manifestation of pediculosis. Pubic lice may infest pubic, perianal, and thigh hair with only a few or with uncountable numbers of nits (Fig. 23-4). The infection load may be particularly severe at the base of the eyelashes. The yellow-gray adults may be difficult to find and are usually located at the base of the hairs, resembling small freckles, scabs, or moles. Blue-black macules (macula cerulea) present in infested areas are associated with chronic infestations.

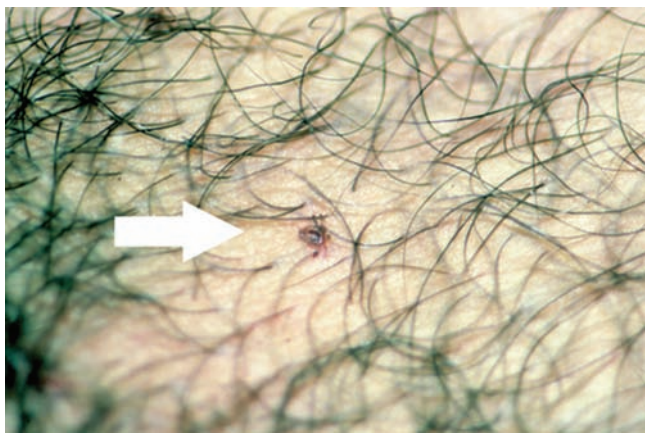


Figure 23-4. Pubic louse (see arrow). (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 23-5. Pediculosis capitis (head louse).

III. WORKUP For all forms of pediculosis, the presence of nits or adult lice is diagnostic (Fig. 23-5). Unexplained pruritus of the scalp should raise suspicion of head lice. Parents or school nurses can screen the posterior scalp with tongue blades or lice combs. It is necessary to be persistent in searching for nits. If suspicion is high, a therapeutic trial or reexamination in 2 to 3 days is indicated. In cases of body lice, close examination of clothing with attention to seams which come in contact with the neck, axillae, or waist may reveal lice or nits. In fastidious individuals, few adult lice and nits will be found, and a careful search—ideally employing a hand lens—should be made, with special attention to the genital area. In cases of public lice, the possibility of coexisting venereal diseases must be considered. Body and axillary hair as well as the eyelashes and beard should also be examined for nits; the scalp may rarely be involved.

IV. TREATMENT First-line topical agents for pediculosis include permethrin, pyrethrins, and malathion. Lindane is considered a second-line agent due to neurotoxicity. Two additional topical agents recently approved by the Food and Drug Administration (FDA) are benzyl alcohol lotion 5% (Ulefsia) and Spinosad 0.9% creme rinse (Natroba), and recently a topical formulation of ivermectin lotion (Sklice) was also approved.

Increasing reports of resistance to permethrin, synthesized pyrethrins, malathion, and lindane have been noted. Besides resistance, other causes of treatment failure include improper technique, noncompliance, or reinfestation. In order to prevent reinfestation, treatment of close contacts is indicated. Most treatments for lice are pediculicidal and work by damaging the nervous

system of the louse. Pediculicides have varying ovicidal activity, and because eggs attached to hair shafts require 7 to 10 days to hatch, a second application is typically needed after this interval to ensure eradication.

The eggs have a thick lipid layer that is difficult to penetrate; a 10-minute application is likely not sufficient to penetrate this membrane. A lice comb with an intertooth space less than the width of the nit is necessary between and after the treatment. Many parents prefer shampoo preparations but, overall, they are less effective than the cream rinse and lotion preparations. A great deal of counseling is required with any infestation as many patients feel socially stigmatized, confused, and distressed with the diagnosis.

All pediculicides kill lice, but the dead organisms do not fall off hairs or the body spontaneously. Most patients regard the continuing presence of dead organisms as evidence of continuing infestation, and it is necessary to clearly instruct them otherwise. The only certain way to remove dead nits is with a fine-toothed comb or forceps. Combs and brushes should be soaked in 2% Lysol or a pediculicidal shampoo for approximately 1 hour or heated in water to approximately 65°C (149°F) for 5 to 10 minutes.

For pediculosis corporis, the patient needs to only wash with soap and water and apply topical antipruritic lotions. If lice get on the body, pediculicides should be used. Lice in clothing may be killed by having the clothes washed and/or dried by machine (hot cycle in each); by boiling, followed by ironing the seams; by dry-cleaning; or by applying dry heat at 140°F (60°C) for 20 minutes.

For infestations of the eyelashes, if only a few lice are present, it may be possible to remove the lice and nits manually with the fingernails or with a nit comb. If further treatment is needed, ophthalmic grade petrolatum ointment applied to the eyelid margins two to four times daily for 10 days is considered the first-line treatment (Table 23-1).

1. Pyrethrins/Permethrin. The traditional treatment of choice for pediculosis capitis or pubis has been pyrethrins with piperonyl butoxide (RID, A-200 Pyrinat) or permethrin (Nix, Elimite); however, observation of increased resistance to these agents has led to more

TABLE 23-1 Primary Treatment Options for Pediculosis	
1.	Pyrethrins/permethrin
2.	Malathion
3.	Benzyl alcohol lotion
4.	Spinosad
5.	Dimethicone
6.	Ivermectin
7.	Trimethoprim–sulfamethoxazole
8.	Lindane
9.	Alternative regimens

frequent use of alternative agents. Pyrethrins, rapid-acting compounds, derived from chrysanthemum plants, are the leading over-the-counter louse remedy. Permethrin is a synthetic pyrethrin. These compounds interfere with neural transmission to the insects, leading to paralysis and death. For both head lice and pubic lice, the medication is applied to affected areas for 10 minutes and then rinsed off. It should not be used more than twice within a 24-hour period. RID and R&C are 0.33% pyrethrin shampoos; A-200 is a 0.33% Pyrinat shampoo and is less ovicidal than the pyrethrins. These products are unstable in heat and light and contraindicated in individuals with known allergy to ragweed, chrysanthemums, or other pyrethrin products, but these reactions are rare.

2. **Malathion.** Malathion lotion 0.5% is rapidly effective against head lice (5 minutes) and is ovicidal (95% killed). The FDA recommended application time is 8 to 12 hours. This organophosphate is one of the least toxic agents, as it is rapidly metabolized by mammalian carboxylesterase. This formulation is marketed in the United States under the name Ovide and is available by prescription; it was previously available as a 1% preparation. It binds slowly to hair but can maintain a residue for 2 to 6 weeks, which helps protect against reinfestation. This product is flammable until dry, and hair dryers and open flames should be avoided. Because of increased resistance to pyrethrin and permethrins, some authors have recommended that malathion be used as a first-line agent.
3. **Benzyl Alcohol Lotion.** Benzyl alcohol lotion 5% (Ulesfia) was approved by the FDA in 2009 for treatment of head lice and works via asphyxiating the louse. The lotion is applied to the scalp for 10 minutes and then rinsed out. Since it is not ovicidal, this must be repeated after 1 week. It can be used in children as young as 6 months of age and in pregnant women.
4. **Spinosad.** In 2011, spinosad 0.9% was approved by the FDA to treat head lice in patients 4 years old and older. Spinosad is derived from actinomycete, *Saccharopolyspora spinosa*, and although its precise mechanism of action is unknown, it appears to function by interfering with louse nicotinic acetylcholine receptors and γ -aminobutyric acid-gated chloride channels, leading to motor neuron excitation, muscular contraction, and eventually paralysis and death. The creme rinse is applied to dry hair and scalp for 10 minutes, followed by rinsing off. Nit combing is not required, and the process can be repeated if live lice are seen 7 days after treatment.
5. **Dimethicone.** Treatment with Dimethicone 4% lotion has been found to be effective in the treatment of head lice. Two treatments are administered 1 week apart and nit combing is performed in between and after treatments. Dimethicone is a silicone oil which is believed to work by coating the louse and interfering with water homeostasis.
6. **Ivermectin.** Recent studies have also demonstrated effectiveness with the use of oral ivermectin in the treatment of pediculosis capitis. In those studies, ivermectin was dosed at 400 $\mu\text{g}/\text{kg}$ (28 mg for 70 kg patient) and given in two doses, 7 days apart. In 2012, the FDA approved Sklice, a formulation of 0.05% ivermectin lotion for the treatment of head lice.

Two recent randomized controlled trials demonstrated good results with a single application of the lotion applied thoroughly to dried hair and rinsed off after 10 minutes.

7. **Trimethoprim–Sulfamethoxazole.** Trimethoprim–sulfamethoxazole (Bactrim, Septra) PO twice daily (or Bactrim DS once daily) for 3 days, repeated in 10 days, seems effective in the treatment of pediculosis capitis. However, because of the risks of severe drug reactions associated with trimethoprim–sulfamethoxazole, this treatment is generally reserved for severe or refractory cases.
8. **Lindane.** γ -Benzene hexachloride (Kwell), a pesticide also known as lindane, is an organochlorine with very slow onset of action and poor ovicidal activity; it takes over 3 hours to kill the lice during which increased lice crawling and twitching can cause increased pruritus for the patient. Lindane is available as a shampoo for the treatment of pediculosis capitis and/or pubis and in cream and lotion form for treating scabies and all forms of pediculosis. Up to 10% of the topically applied drug may be absorbed percutaneously, and therefore it should be applied to the skin after it has completely dried; alternative treatments should be considered in infants, young children, pregnant women, and individuals with significant alteration in epidermal barrier function (i.e., erythroderma). Due to concern for potential neurotoxicity, in 2003 the FDA recommended considering lindane as a second-line treatment for pediculosis, and in a separate update, the American Academy of Pediatrics no longer recommends lindane as a treatment option in children.
9. **Alternative Regimens.** Parents have undertaken alternative therapies because of fear of use of pesticides and frustration with treatment failures. Products with an oil base (Vaseline, olive oil, mayonnaise, and margarine) may smother the adult lice, but have no effect on the nits. Dippity-Do styling gel applied overnight under a shower cap is water soluble and is reported to smother lice. Vinegar or formic acid has been reported to remove the glue that holds the nit firmly to the hair shaft. Detanglers, plant oils, and cream rinses will also help lubricate the hair shaft and remove nits. Alcohol, kerosene, and paint thinners have also been used but carry extreme risks.

SCABIES

- I. **BACKGROUND** Scabies is caused by infestation with the mite *Sarcoptes scabiei* var. *hominis*. *Sarcoptes scabiei* has four pairs of legs and transverse corrugations and bristles on its dorsal aspect. The female mite, just visible to the human eye, excavates a burrow in the stratum corneum and travels as much as 5 mm every day for 1 to 2 months before dying. The eggs she lays, which hatch in approximately 1 week, reach maturity in approximately 3 weeks, and start a new cycle. Most infected adults will harbor 10 to 12 mites on their skin. Infestation with scabies is common in chronic care facilities, and live mites may be isolated from even dust and fomites.

Scabies is acquired principally through close personal contact but may be transmitted through clothing, linens, furniture, or towels. The female can survive away from humans for at least 96 hours. The incubation period is

usually <1 month but can be as long as 2 months. *Sarcoptes scabiei* has cross-antigenicity with the house dust mite; this may play a role in the susceptibility to scabies and its clinical manifestations.

II. CLINICAL PRESENTATION Scabies infestation is noted for severe itching, which becomes most marked shortly after the patient goes to bed or for children during naptime. The severe pruritus is probably caused by an acquired sensitivity to the organism and its saliva, eggs, and feces and is first noted 3 to 4 weeks after primary infestation but sooner (24 to 48 hours) in subsequent infections. Pruritus may be delayed or overlooked in the immunocompromised or elderly patient. Early in the course, only the sites of burrows are pruritic; later, the itching may become generalized. The intense itching leads to scratching-induced erosions and bloody excoriations. Sites of involvement are chiefly the interdigital webs of the hands, wrists, antecubital fossae, points of the elbows, nipples, umbilicus, lower abdomen, genitalia, and gluteal cleft (Fig. 23-6). Lesions of the glans penis and scrotum are characteristic in males and may appear as flesh- to pink-colored papules and nodules (Fig. 23-7). These lesions are slow to resolve even following treatment. Infants and small children often have lesions on the palms, soles, head, and neck. Because of the extremely narrow differential diagnosis, pustules on the palms of an infant should be considered scabies until proven otherwise. Generalized urticarial papules, excoriations, and eczematous changes are secondary lesions caused by sensitization to the mite. These secondary lesions may persist for weeks even after eradication of the infestation has occurred.

Crusted or Norwegian scabies is a variant that occurs in debilitated, elderly, or immunocompromised patients. It is characterized by a generalized dermatitis with crusted hyperkeratosis of the palms and soles that lead to deep fissures (Fig. 23-8). Because the skin is infested with thousands of mites, this variant of

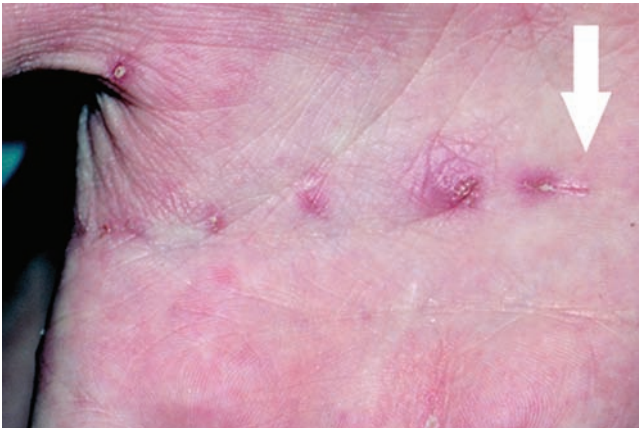


Figure 23-6. Scabies. This close-up view shows a burrow (arrow) on the palm. (With permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 23-7. Scabies. Pruritic papules and nodules are present on the penis and scrotum. (With permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 23-8. Norwegian scabies. This child with Down syndrome has verrucous plaques on his hands and thickened dystrophic nails. The lesions are teeming with mites. (With permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

scabies is highly contagious. Patients with HIV disease may present with scabies as their first AIDS defining illness.

III. WORKUP The diagnosis of scabies is primarily clinical and can be a difficult conclusion at which to arrive. Characteristic burrow may be visualized as multiple straight or S-shaped ridges or dotted lines, 5 to 20 mm long. Mites are also in papules and vesicles, the most common lesions.

The diagnosis of scabies can also be made by demonstrating the presence of the organisms, the eggs, or the oval, brown-black fecal concretions (called **scybala**) by light microscopy (Fig. 23-9). A superficial epidermal scraping of a burrow or papule is the best method for obtaining a specimen. Apply a thin layer of mineral oil to the burrow or papule, then gently scrape with a no. 15 blade. Place the material recovered on a glass slide, cover with immersion oil, and examine under scanning power.

IV. TREATMENT (Table 23-2)

A. Permethrin is a synthetic pyrethroid that interferes with the influx of sodium through cell membranes, leading to neurologic paralysis and death of the mite. There is minimal percutaneous absorption (<2%), which is

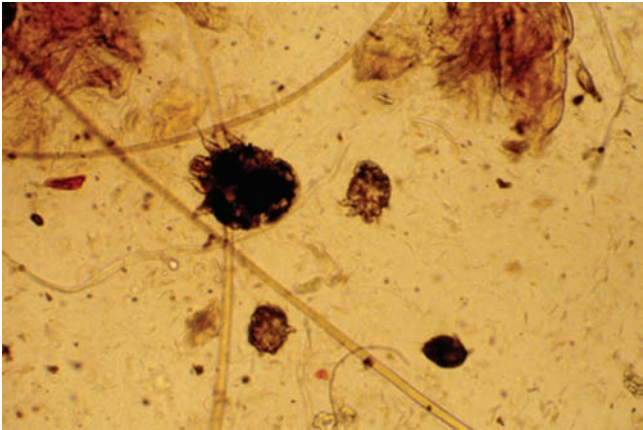


Figure 23-9. Scabies. Mites, ova, and fecal pellets are shown. (With permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

TABLE 23-2	Primary Treatment Options for Scabies
<ul style="list-style-type: none"> - Permethrin 5% cream/lotion - Ivermectin orally 200 µg/kg - Lindane 1% cream/lotion 	

TABLE 23-3 Treatment Procedure with Permethrin

1. Apply permethrin cream from chin to toe, especially in skin folds and webspaces overnight
2. Wash off the medicine next morning, approximately 8 h later
3. Repeat the same treatment in 1 wk
4. Wash and dry all clothing in hot cycle
5. Personal items can be sealed in plastic bags for 10 d
6. All persons in close contact should be considered for treatment

rapidly hydrolyzed and excreted in the urine. Permethrin 5% dermal cream (Elimite) is applied for 8 to 12 hours (typically overnight) to the entire body from the chin down then washed off (Table 23-3). Particular attention must be paid to the interdigital webs, wrists, elbows, axillae, breasts, buttocks, umbilicus, and genitalia. Mites can take up residence under the nails, too, so they should be trimmed and treated. Burning and stinging with application have been reported especially in more severe infestations. A second application may be performed as a precaution 1 week later or if there is clear evidence of treatment failure. Permethrin 5% has a higher cure rate and less potential toxicity than lindane. Elimite is classified as a pregnancy category B agent and has been safely administered in children as young as 2 months of age. Cases of lindane-resistant scabies have been eradicated with this preparation; no cases of permethrin resistance have been reported to date.

- B. Apply Lindane 1% (Kwell) Cream or Lotion** to dry skin of the entire body from the chin down. Medication should be applied for 8 to 12 hours and then washed off. Lindane is a central nervous system (CNS) stimulant that produces seizures and death in the mite; it can also cause neurotoxicity in humans if the recommended dose is exceeded or if there is increased absorption through inflamed or fissured skin or a susceptible host. Lindane should be avoided in pregnant or nursing women (although it is pregnancy category class B), infants, young children, or individuals with seizure disorders or other neurologic disease. Cure rates of 90% have been reported with a single treatment of lindane but because of resistance, careful follow-up, and a possible second treatment should be considered.
- C. Ivermectin** is a very effective antiparasitic agent. A single oral dose of 200 µg/kg is generally effective in uncomplicated cases of scabies with resolution of pruritus within 48 hours. It is likely that a second dose in 1 week is required in many patients. This drug is not toxic to humans unless it crosses the blood–brain barrier; therefore, it should not be used in children who weigh <15 kg or in women during pregnancy or breast-feeding. Although not approved by the FDA for this indication, this may be a very promising treatment for epidemics of scabies, the infirm, or highly infested individuals. Resistance has been documented in the veterinary literature but not in humans.
- D. Precipitated Sulfur 6%** in a water-washable base (or in petrolatum, which is messier), applied nightly for three nights and washed off 24 hours after

the last application remains a useful treatment. Patients may complain of the sulfur odor, messiness, and staining of bed linen. This treatment is often chosen for infants younger than 2 months of age and pregnant and lactating women, although sulfur, too, has produced toxicity and death in infants.

E. Other Considerations

1. **Clothing** should be thoroughly washed and/or dried by machine (hot cycle in each) or dry-cleaned and linen and towels changed; personal articles can be sealed in a plastic bag for 10 days. In hot and sunny climates, linens may be left out in the hot sun for 4 to 6 hours to destroy any mites or eggs that may reside within. Family, close friends, sexual contacts, and those sharing quarters of patients with scabies should all be considered for treatment to prevent reinfection or a small epidemic. Transmission of scabies is unlikely after 24 hours of treatment.
2. **Persistent Itching** in treated scabies may be caused by continued infestation, a slowly subsiding hypersensitivity response, or irritation from medication. Four weeks is sufficient time to reevaluate for persistent infestation following treatment. If mites are still present, retreat and consider using a different method than what was first tried. Persistent pruritic nodules may remain in patients otherwise seemingly cured of scabies. These lesions are similar to prurigo (neurodermatitis) nodules and respond only to intralesional corticosteroid injection.

TICKS

I. BACKGROUND Ticks are small arachnid ectoparasites that survive by feeding on blood from animal and human hosts. They are commonly found in tall grasses and wooded areas. After attaching to the human skin, the female tick feeds, becomes engorged after 7 to 14 days, and then drops off. The three most medically important ticks in the United States are the lone star tick (*Amblyomma americanum*), *Dermacentor*, and *Ixodes* ticks. The lone star and *Dermacentor* ticks are vectors that can transmit Rocky Mountain spotted fever (RMSF) (*Rickettsia rickettsii*), ehrlichiosis (*Ehrlichia chaffeensis*), and tularemia (*Francisella tularensis*). *Ixodes* ticks (commonly known as deer ticks) can transmit Lyme disease (*Borrelia burgdorferi*), anaplasmosis (*Anaplasma phagocytophilum*), and babesiosis (Fig. 23-10).

Lyme disease is increasingly prevalent in many areas of the United States and can occur as a co-infection with anaplasmosis or babesiosis. Early Lyme disease is categorized into localized (stage 1) and disseminated (stage 2) types. The localized rash, erythema migrans (EM) develops at the site of the tick bite in 80% to 90% of symptomatic patients within 3 to 32 days of the bite.¹ The tick bite is often not recognized. Systemic symptoms such as fatigue, arthralgias, myalgias, headache, stiff neck, and anorexia are present in most patients with EM (Table 23-4). Disseminated disease indicates spread of the disease to other organs, usually with CNS, cardiac, or rheumatologic symptoms. Late disease (stage 3) occurs in untreated individuals with manifestations involving the CNS and/or the musculoskeletal system such as Bell palsy and polyarthritis.

RMSF, though less common, can range in severity from fever and rash to severe illness with multiorgan system involvement, coma, cardiovascular compromise, and death. This disease is found throughout the United States but



Figure 23-10. Deer ticks at the larval, nymphal, and adult stages, measuring 0.5, 1, and 3 mm long, respectively. Included in this photo is a sewing needle to provide scale.

TABLE 23-4 Differential Diagnosis for Erythema Migrans	
Tick-bite or insect-bite hypersensitivity reaction	
Bacterial cellulitis	
Erysipelas	
Erythema multiforme	
Southern tick-associated rash illness	
Tinea	
Nummular eczema	
Granuloma annulare	
Contact dermatitis	
Urticaria	
Fixed drug eruption	
Pityriasis rosea	
Parvovirus B19 infection in children	

is most common in the southeastern states. Following an infected tick bite, *R. rickettsii* invade endothelial cells of small vessels leading to a multisystem vasculitis. After an incubation period of approximately 6 to 8 days, patients develop an abrupt onset of fever, headache, myalgias, nausea, and vomiting.

Skin findings develop a few days after the fever with characteristic rash beginning on the extremities before generalizing. Multiple organ systems are often involved in RMSF, and patients may present with hepatosplenomegaly, respiratory distress, abdominal pain, and neurologic manifestations such as meningitis, seizures, and cranial nerve palsies (Table 23-5). The typical course of the illness is about 2 to 3 weeks and has a mortality of less than 2% if treated within the first 4 days of illness and 5.3% for those beginning treatment on day 5 or later.² When fatal, most patients succumb rapidly within the first week.

II. CLINICAL PRESENTATION Tick bites are painless and often go unnoticed unless itching develops, or the tick becomes engorged. The engorged tick, often the size of a large pea, may resemble a vascular tumor or wart, while the nonengorged tick may be mistaken for a mole (Fig. 23-11).

- The tick-bite site may not be identifiable or may be marked by an eschar.
- Previously sensitized hosts may develop a localized urticarial response.
- The usual bite reaction shows a small papule or dermal nodule surmounted by a necrotic center.
- Granulomatous response to tick bites causes lesions that resemble dermal fibromas (dermatofibroma and histiocytoma).
- The rash of localized Lyme disease, EM, starts as an erythematous macule/papule that gradually expands over days taking on an annular configuration often 5 to 7 cm in diameter (Fig. 23-12). The outer border is erythematous; the center can have clearing, or appear dusky, violaceous, vesicular, or necrotic. It is often accompanied by a burning sensation and occasionally pain or pruritus. Early in the disease process, the rash may appear homogeneous without central change. Multiple secondary lesions can be observed in 25% to 50% of patients indicating disseminated disease. Palm and sole involvement does not occur in contrast to RMSF.
- Constitutional symptoms can be associated with early-stage Lyme disease. If Lyme disease is not treated in the early stage, chronic arthritis and neurologic and cardiac complications may develop such as meningitis, heart blocks, and carditis.
- The characteristic rash of RMSF begins with erythematous macules on the wrists and ankles that become papular and spread to the palms and soles

TABLE 23-5	Differential Diagnosis for Rocky Mountain Spotted Fever
Meningococcemia	
Human monocytic ehrlichiosis	
Drug eruptions	
Mononucleosis	
Viral exanthema	
Vasculitis	
Toxic shock syndrome	
Kawasaki disease	

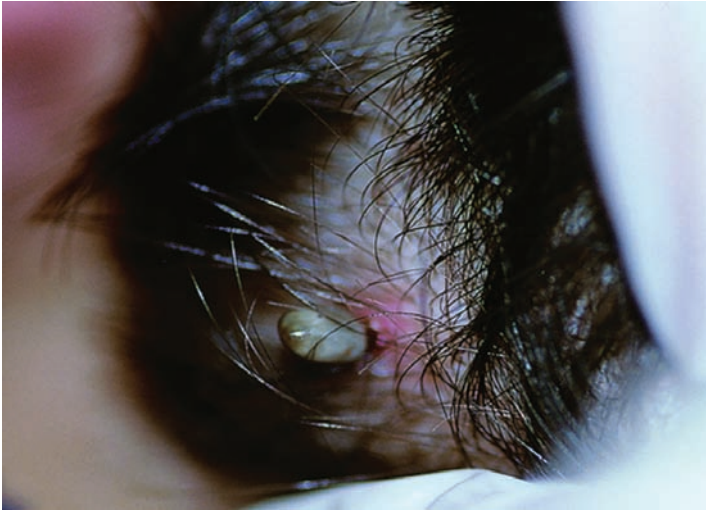


Figure 23-11. Tick bite illustrating the appearance of an engorged tick. (From Fleisher GR, Ludwig S, Baskin MN. *Atlas of Pediatric Emergency Medicine*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)



Figure 23-12. Erythema migrans of acute Lyme disease with target-like concentric rings. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 23-13. Characteristic rash of Rocky Mountain spotted fever. (Courtesy of Sidney Sussman, MD.)

within hours before generalizing (Fig. 23-13). This blanchable rash becomes petechial over the course of 2 to 4 days. As the rash resolves over the course of 2 to 3 weeks, the areas gradually fade or may develop postinflammatory hyperpigmentation.

III. WORKUP

A. Lyme Disease. Lyme disease is a clinical diagnosis in the presence of EM. Additional acute symptoms or history of recent tick bite helps to solidify the diagnosis. Laboratory confirmation is a two-step process:

1. Sensitive enzyme-linked immunosorbent assay (ELISA)
2. Confirmatory western blot for serum IgM and IgG in patients with positive or equivocal ELISAs

Serologic confirmation is complicated by relatively high background rates of seropositivity, reaching more than 4% in endemic areas in the United States. Therefore, a positive serologic test does not guarantee active Lyme borreliosis. A negative test similarly does not rule out Lyme disease due to the low sensitivity in early disease. It may be necessary to repeat serologic testing after 2 to 6 weeks. Lyme polymerase chain reaction (PCR) is also available for cerebrospinal fluid or joint fluid for patients that demonstrate CNS or musculoskeletal symptoms. Skin biopsy culture or PCR can also be useful. Coinfection of Lyme

disease with anaplasmosis or babesiosis often presents with leukopenia and thrombocytopenia. Additional nonspecific findings include elevated erythrocyte sedimentation rate, elevated IgM, mild anemia, and elevated liver enzymes.

B. Rocky Mountain Spotted Fever. RMSF is also a clinical diagnosis based on the classic triad of fever, rash, and tick bite; however, the complete triad is only found in about one-half of patients with RMSF. Confirmation of diagnosis is made via a positive serologic test for antirickettsial antibodies or a positive ELISA in a patient with correlating clinical course. Serologic conversion does not occur until the second week of infection; therefore, it is vital that a high index of suspicion is maintained and that empiric antibiotics are administered if the disease is suspected. Nucleic acid testing by PCR for *R. rickettsii* is occasionally available and can be performed on blood, tissue biopsy specimens, and ticks but is less sensitive than serologic testing. Immunohistochemical staining of skin biopsy specimens is accurate but rarely performed. Patients with RMSF may also have thrombocytopenia, elevated liver enzymes, hyponatremia, and leukocyte abnormalities.

IV. PREVENTION Protection against tick infestation is best accomplished by avoiding tick-infested areas, covering the skin with long-sleeved clothing, and applying insect repellants with diethyltoluamide. Use the recommended amount of insect repellant but avoid frequent reapplications; do not use repellants on infants; on the hands or face of young children; or on cuts, abrasions, or sunburned skin. Daily skin checks should be recommended for patients that are active outdoors, especially in forested areas. Proper tick removal involves grasping the tick as close to the skin as possible and applying gentle traction. It is important not to irritate the organism (with nail polish or heated match stick) or crush the organism while it is being taken off the skin as this can increase the risk of transmission of infected materials. Removal of a tick within 24 to 36 hours of attachment makes the transmission of infectious material unlikely.

Two Lyme disease vaccinations were briefly available in the late 1990s and shown to be moderately successful; however, these were withdrawn from the market several years later due to poor market success.

Antibiotic chemoprophylaxis has been shown to decrease the likelihood of developing Lyme borreliosis after the removal of an *Ixodes scapularis* tick. One 200 mg dose of doxycycline was 87% effective in preventing EM at the tick site and should be administered within 72 hours of tick removal for patients in high-risk areas.¹

V. TREATMENT

A. Treatment Recommendation for Lyme Borreliosis (Table 23-6)

1. **Early Lyme Disease** (for adult patients or children >8 years of age without neurologic, cardiac, or joint involvement).
 - a. **Doxycycline** 100 mg two times per day for 10 to 21 days. Also effective against anaplasmosis and RMSF.
 - b. **Amoxicillin** 500 mg three times daily for 14 to 21 days. Treatment of choice for children under age 8 years and pregnant women.
 - b. **Cefuroxime** 500 mg daily for 14 to 21 days.
 - d. **Azithromycin** 500 mg daily for 7 to 10 days (less effective).

TABLE 23-6 Primary Treatment Options for Lyme Disease

1. Doxycycline
2. Amoxicillin
3. Cefuroxime

TABLE 23-7 Primary Treatment Options for Rocky Mountain Spotted Fever

1. Doxycycline
2. Chloramphenicol

2. Treatment of Meningitis, Arthritis, and Carditis, or of the Immunocompromised Patient is beyond the scope of this text, and guidance should be sought from an infectious disease specialist.

B. Treatment Recommendation for Rocky Mountain Spotted Fever (Table 23-7)

- 1. Empiric Treatment** should be started immediately if RMSF is suspected as most fatal cases occur within the first week of infection. Treatment consists of doxycycline 100 mg twice daily for 7 days or at least 48 hours after fever resolves. This is currently the treatment of choice for adults as well as children aged less than 9 years as dental staining has not been associated with short courses of doxycycline.²
- 2. Alternative Therapy.** Chloramphenicol 50 to 75 mg/kg/day (no longer available).

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REFERENCES

1. Stanek G, Wormser GP, Gray J, Strie F. Lyme borreliosis. *Lancet*. 2012;379(9814):461-473 [Epub September 6, 2011].
2. Minnietar TD, Buckingham SC. Managing Rocky Mountain spotted fever. *Expert Rev Anti Infect Ther*. 2009;7(9):1131-1137.

Suggested Readings

- Bouvresse S, Chosidow O. Scabies in healthcare settings. *Curr Opin Infect Dis*. 2010;23:111-118.
- Burgess IF. Pediculosis. *J Am Acad Dermatol*. 2004;50:1-12.
- Elston DM. Drugs used in the treatment of pediculosis. *J Drugs Dermatol*. 2005;4:207-211.
- Frankowski BL. American Academy of Pediatrics guidelines for the prevention and treatment of head lice infestation. *Am J Manag Care*. 2004;10:S269-S272.

- Grabowski G, Kanhai A, Grabowski R, et al. Norwegian scabies in the immunocompromised patient. *J Am Podiatr Med Assoc.* 2004;94:583-586.
- Huynh TH, Norman RA. Scabies and pediculosis. *Dermatol Clin.* 2004;22:7-11.
- Karthikeyan K. Treatment of scabies: newer perspectives. *Postgrad Med J.* 2005;81:7-11.
- Karthikeyan K. Crusted scabies. *Indian J Dermatol Venereol Leprol.* 2009;75:340-347.
- Keller EC, Tomecki KJ. Cutaneous infections and infestations: new therapies. *J Clin Aesthet Dermatol.* 2011;4(12):18-24.
- Ko CJ, Elston DM. Pediculosis. *J Am Acad Dermatol.* 2004;50:1-12.
- Lebowhl M, Clark L, Levitt J. Therapy for head lice based on life cycle, resistance, and safety considerations. *Pediatrics.* 2007;119:965-974.
- Meagher KE, Decker CF. Other tick-borne illnesses: tularemia, Colorado tick fever, tick paralysis. *Dis Mon.* 2012;58(6):370-376.
- Pariser D, Meinking T, Bell M, Ryan W. Topical 0.05% ivermectin for treatment of head lice. *N Engl J Med.* 2012;367:1687-1693.
- Piesman J, Beard CB. Prevention of tick-borne diseases. *J Environ Health.* 2012;74(10):30-32.
- Romanelli F. Treatment-resistant scabies and lice infections. *JAAPA.* 2002;15:51-54.
- Steen CJ, Carbonaro PA, Schwartz RA. Arthropods in dermatology. *J Am Acad Dermatol.* 2004;50:819-842.
- Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Disease Society of America. *Clin Infect Dis.* 2006;43(9):1089-1134.

I. BACKGROUND Intertrigo is a nonspecific inflammatory dermatosis involving the opposing skin of body folds. It is found principally in the inframammary, axillary, inguinal, and gluteal folds, but it may also affect other similar areas such as folds of the neck creases, antecubital fossae, and umbilical and interdigital areas. Patients with diabetes mellitus are also prone to developing intertrigo. Intertrigo can arise as a result of skin constantly rubbing on skin, heat, moisture, and friction, which can all lead to maceration, inflammation, and often secondary bacterial or fungal infections with *Streptococcus* in infants or *Candida albicans*, respectively (Fig. 24-1). In tropical regions, the genitocrural and perianal areas may be colonized with *Trichosporon beigelii*.

II. CLINICAL PRESENTATION Early stage and mild intertrigo are associated with soreness or itching (Fig. 24-2). Incontinence may contribute to intertrigo in several ways: excessive moisture, irritating chemicals present in urine and feces, microbial contamination, and altering skin surface pH. Intertrigo is one form of diaper dermatitis in infants and is characterized by erythema only in skin folds, without pustules; it is most likely a primary irritant



Figure 24-1. Candida intertrigo after a course of oral antibiotics in a 1-year-old child. (Owen Laboratories, Inc.) (Sauer GC, Hall JC. *Manual of Skin Diseases*. 7th ed. Philadelphia, PA: Lippincott-Raven; 1996.)



Figure 24-2. Intertrigo (intertriginous seborrheic dermatitis). This patient has an itchy erythematous rash in his inguinal creases. This condition is frequently confused with tinea cruris and cutaneous candidiasis. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003, with permission.)

reaction with possible low-grade infection. Some intertriginous eruptions have been reported in pediatric patients undergoing chemotherapy. Other eruptions that localize in the body folds and must therefore be differentiated from simple intertrigo include seborrheic dermatitis, psoriasis (inverse type), dermatophyte infections, erythrasma, irritant dermatitis, and miliaria.

Mild erythema is seen initially; the red well-demarcated plaques oppose each other on each side of the skin fold, almost in a mirror image. This may then progress to more intense inflammation with erosions, oozing, exudation, and crusting. Painful fissures may develop within these erythematous plaques. Finally, vegetative changes, overt purulence, and surrounding cellulitis may arise in these areas.

Intense erythema with satellite papules and pustules is suggestive of infection with *C. albicans*, while sharply margined plaques suggest an inflammatory, noninfectious dermatosis. Macerated skin may become colonized with bacteria and then become malodorous. Incontinent patients with diaper dermatitis may develop nodules in the perianal, suprapubic, buttock, and crural fold areas.

III. WORKUP

1. Examine pustule contents or scales microscopically with potassium hydroxide (KOH) preparation and examine culture for evidence of bacterial, *Candida*, or dermatophyte infection.
2. Examine the skin using a Wood lamp for evidence of coral-red fluorescence suggestive of erythrasma.
3. Initiate investigation for and treatment of associated medical conditions such as diabetes, obesity, and incontinence.

IV. TREATMENT

A. Lifestyle Changes

1. Living and working areas should be cool and dry. Air-conditioning or fans will help. Have the patient disrobe for at least 30 minutes b.i.d. and expose the involved folds to a hair dryer or fan to promote drying.
2. Wash, rinse, and dry intertriginous areas at least twice daily, preferably with a mild antibacterial or low pH cleanser (pH 5.5 to 7). Use a hair drier to ensure that the folds are totally dry. Liberally apply a talc-containing powder.
3. Clothing should be light, nonconstricting, and absorbent. Avoid wool, nylon, and synthetic fibers. Bras should provide good support and not rub against the skin.
4. Avoid occlusive, oily, or irritating ointments or cosmetics.
5. In certain instances of incontinence, the benefit from a protective ointment may outweigh the potential harm.
6. Careful and prompt attention to soiling by incontinent patients is mandatory.
7. Avoid prolonged sitting and driving.
8. Weight loss should be encouraged.

B. Specific Measures

1. Apply cool tap water or Burow solution (aluminum acetate) compresses or soaks t.i.d. to q.i.d. to exudative areas.
2. Separate folds with absorbent material, for example, cotton sheeting well dusted with drying powders. Cornstarch should not be used, since it may encourage bacterial and fungal overgrowth. Zeasorb powder with or without miconazole (Zeasorb-AF) absorbs excess moisture and decreases friction in skin folds.
3. Initially, corticosteroid or steroid-antibiotic lotions, creams, or gels, such as triamcinolone mixed with silver sulfadiazine, should be applied b.i.d. to t.i.d. for up to 2 weeks. Prolonged use of these topical medications should be avoided because continued application of fluorinated steroids may lead to intertriginous striae and cutaneous atrophy. Over-the-counter hydrocortisone (1%), which is nonfluorinated, will usually be effective, without the corticosteroid side effects.
4. Bland lotions (calamine) are soothing and drying.
5. Some physicians apply drying antiseptic dye preparations to these areas and instruct patients to use them once daily thereafter. One-half- or full-strength Castellani paint or 0.5% to 1.0% gentian violet solution may be used. These dyes are very effective but messy and may sting or burn on application.
6. Specific treatment for *C. albicans*, dermatophytes, or bacteria may be helpful in cases where the organism has been demonstrated.
7. Botulinum toxin injections may be necessary to treat hyperhidrosis, which can exacerbate intertriginous eruptions.

ACKNOWLEDGMENTS

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Suggested Readings

- Garcia H. Dermatological complications of obesity. *Am J Clin Dermatol*. 2002;3:497-506.
- Guitart J, Woodley D. Intertrigo: a practical approach. *Compr Ther*. 1994;20:402-409.
- Mistiaen P, Poot E, Hickox S, et al. Preventing and treating intertrigo in the large skin folds of adults: a literature overview. *Dermatol Nurs*. 2004;16:43-46, 49-57.
- Neri I, Savoia F, Giacomini F, Patrizi A. Streptococcal intertrigo. *Pediatr Dermatol*. 2007;24(5):577-578.
- Santiago-et-Sánchez-Mateos JL, Beà S, Fernández M, Pérez B, Harto A, Jaén P. Botulinum toxin type A for the preventive treatment of intertrigo in a patient with Darier's disease and inguinal hyperhidrosis. *Dermatol Surg*. 2008;34(12):1733-1737.
- Webber KA, Kos L, Holland KE, Margolis DA, Drolet BA. Intertriginous eruption associated with chemotherapy in pediatric patients. *Arch Dermatol*. 2007;143(1):67-71.
- Wolf R, Oumeish OY, Parish LC. Intertriginous eruption. *Clin Dermatol*. 2011;29(2):173-179.

I. BACKGROUND Keloids and hypertrophic scars (HSs) represent an excessive and aberrant healing response to cutaneous injuries, such as acne, trauma, surgery, and piercing. Both are seen in all races, especially in individuals with dark skin. Common anatomic sites for both HSs and keloids include the earlobes, chest, lower legs, and upper back. In general, HSs remain in the area and shape of original injury, whereas keloids expand beyond the site of initial trauma and can be recalcitrant to treatment.

The pathogenesis of HSs and keloids is unclear. Fibroblasts from HSs and keloids demonstrate excessive proliferative and low apoptosis properties. In addition to the increasing production of collagen, fibroblasts from HSs and keloids also produce an increased amount of elastin, fibronectin, and hyaluronic acid. Tumor growth factor- β (TGF- β) appears to play a central role in the pathogenesis as evidence indicates that TGF- β isoforms 1 and 2 are particularly involved in collagen synthesis promotion and scarring, while isoform 3 is involved in scar prevention.

II. CLINICAL PRESENTATION Keloids are usually asymptomatic, although some are pruritic and others may be quite painful and tender (Figs. 25-1 and 25-2). Occasionally, there may be a functional impairment if the scar interferes with movement of the involved area. Keloids start as pink



Figure 25-1. Keloid at ear-piercing site. (From Rubin E, Farber JL. *Pathology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.)



Figure 25-2. This lesion is growing well beyond the border of the cesarean section scar.

or red, firm, well-defined, telangiectatic, rubbery plaques that grow beyond the boundaries of the original wound and may become smoother, irregularly shaped, hyperpigmented, firm, and symptomatic.

HSs appear as scars that are more elevated, wider, or thicker than expected and are confined within the size and shape of the inciting injury (Figs. 25-3 and 25-4).

III. WORKUP The diagnosis of keloids and HSs is usually made with clinical observation; a biopsy will confirm the diagnosis. The patient may give a history of previous trauma, while keloid formation can develop spontaneously with dermatologic diseases like Rubinstein-Taybi and Goeminne syndromes. Other causes, if present, should be investigated and treated aggressively including dissecting cellulitis of the scalp, acne vulgaris, acne conglobata, hidradenitis suppurativa, pilonidal cysts, foreign-body reactions, and local infections with herpes virus or vaccinia virus (Table 25-1).

IV. TREATMENT HSs usually require no treatment and often resolve spontaneously in 6 to 12 months. Intralesional corticosteroid injection is an effective treatment, and excision is another viable option because most HSs do not recur. Pulsed dye laser (PDL) (585 to 595 nm) surgery is also another effective modality; the laser treatment decreases redness and scar mass and improves subjective symptoms. Some clinicians feel that the combination of intralesional steroid and PDL is more effective than either used alone. Keloids are much more difficult to treat because they are not only recalcitrant to various therapeutic modalities but also have a high rate of recurrence (Tables 25-2 and 25-3).

A. Prophylactic Considerations are of paramount importance. Optional elective surgical procedures must be avoided in individuals prone to keloid



Figure 25-3. Hypertrophic scars characteristic of acne scars that occur on the trunk. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 25-4. Hypertrophic scars in healed deep partial-thickness burns cause considerable patient discomfort and misery due to the itching, warmth, raised appearance, and often functional limitations. (From Mulholland MW, Lillemoe KD, Donerty GM, et al. *Greenfield's Surgery Scientific Principles and Practice*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)

TABLE 25-1	Differential Diagnosis
<ul style="list-style-type: none">• Dermatofibroma• Dermatofibrosarcoma protuberans• Foreign-body reaction• Lobomycosis• Sarcoidosis	

TABLE 25-2	Primary Treatment Options
<ol style="list-style-type: none">1. Intralesional corticosteroids2. Surgical excision3. Combination approach (using intralesional steroids in combination with cryosurgery, please refer to table 25-3)	

TABLE 25-3	Common Treatment Options at a Glance
Treatment	Comments
Intralesional steroids	May be used in combination with cryosurgery, pulsed dye laser, 5-fluorouracil, and surgery
Silicone gel sheeting	May be used in combination after surgery or other therapeutic modalities
Cryo	May be used in combination with intralesional corticosteroids
Surgery	May be used in combination with intralesional corticosteroids, 5-fluorouracil, radiation, and imiquimod
Laser	Pulsed dye laser and fractional nonablative and ablative lasers

formation. When surgery is necessary for cosmetic reasons, early childhood is the best time. Scalpel surgery with strict aseptic technique and avoidance of wound tension is mandatory. Electrosurgery and chemosurgery should be avoided; cryosurgical procedures are usually not followed by keloid formation. Surgical procedures should be avoided in patients who have been treated with isotretinoin within the past 6 to 12 months because of an increased risk of keloid and HS formation.

B. Intralesional Corticosteroid Injection often brings excellent results and is the first-line treatment. In skin fibroblast culture, glucocorticoids specifically decrease collagen synthesis and may enhance collagen breakdown in keloids.

1. Depending on the anatomic location, the use of high concentrations of medication (triamcinolone acetonide or diacetate, 10, 25, or 40 mg/mL) injected undiluted at 4- to 6-week intervals is warranted. Multiple injections directly into the bulk of the mass over several months (to years) may be necessary. Overtreatment may lead to atrophy.
 2. Initially, injection may be difficult through the tough collagenous mass; however, with continued treatment the keloid softens, allowing easier administration. Freezing the keloid with liquid nitrogen before injection causes the lesion to become edematous and less dense, allowing the corticosteroid to be injected with ease and accuracy. In addition, the freezing itself can have a therapeutic effect equal to that of the injected corticosteroids. Treatment with the PDL before injection may be additive or synergistic in bringing about improvement from each approach.
 3. Injections at more frequent intervals may result in a depressed, atrophic lesion.
 4. Injection with a combination of 5-fluorouracil (5-FU) with triamcinolone acetonide, for a final concentration of 5 mg/mL 5-FU (9:1 dilution of 50 mg/mL 5-FU to a 10 mg/mL triamcinolone) has met with success in the management of keloids. This combination is more painful on injection than corticosteroids alone. Inject one to two times a week initially and then decrease to monthly intervals.
- C. Silicone Gel or Occlusive Sheeting** applied for 12 to 24 hours daily for 8 to 12 weeks or longer, without pressure, to HSs or keloids, has led to moderate success rates in small lesions. The mechanism of the treatment is unclear. Sheets (Topigel, Sil-K, Band-Aid Brand Scar Healing Strips, Curad Scar Therapy, and Scarguard) are cut to size and held in place with paper tape or other adhesive. This treatment has very few side effects, and it is one of the few treatments that patients can actively self-administer in between office-based treatments such as intralesional steroid or cryotherapy. Compression or pressure devices are alternatives for home treatment. Often, a minimum of 4 to 6 months of treatment is needed to see some benefit.
- D. Cryosurgery** at monthly intervals may be effective for treating small lesions. Theoretically, cryotherapy causes ischemia that lead to subsequent necrosis and flattening of the tissue. Treat with two to three freeze–thaw cycles of 30 seconds each. Local anesthesia may be necessary. Complications include pain, edema, hypoesthesia, and hypopigmentation. The latter complication makes cryotherapy a less favorable treatment option for patients with dark skin colors.
- E. Surgical Excision** is perhaps the only effective modality in converting broad-based keloid scars into narrow and cosmetically acceptable scars. However, excision alone leads to 50% to 100% recurrence. Hence, adjunctive treatments, such as intralesional steroid, radiation, or even topical imiquimod, after surgical debulking are always needed to reduce the recurrence rate. The common **x-ray radiation** regimen is 900 cGy or greater given in fraction within 10 days of surgery. The combination of radiation with surgery can prevent recurrence in approximately 75% of patients at 1-year follow-up.

F. Laser Therapy including PDL and fractional laser resurfacing are both employed for the treatment of HSs and keloids. In a number of controlled trials, **PDL (585 nm)** has been shown to improve subjective symptoms and reduce erythema and height of keloidal scars. Fractional nonablative (1,540 nm) and ablative CO₂ laser resurfacing of thermal burn scars showed significant improvement in texture with thinner scars and thicker scars, respectively. Subsequent dermal remodeling is believed to contribute to the improved skin texture and pliability seen in the treatment of scars.

G. Other Therapies have been investigated for the treatment of HSs and keloids, which include compression, collagenases, interferon- γ (IFN- γ) and IFN- α -2b, imiquimod, retinoic acid, ultraviolet A1, intralesional bleomycin, mitomycin-C, tamoxifen citrate, methotrexate, imidazoquinoline, calcineurin inhibitors, phenylalkylamine calcium channel blockers, botulinum toxin, vascular endothelial growth factor inhibitors, hepatocyte growth factor, basic fibroblast growth factor, interleukin-10, manosa-6-phosphate, transforming growth factor- β , antihistamines, and prostaglandin E2, verapamil. Although some of these treatment modalities have been reported more often than others, consensus in treatment regimens is lacking due to the limited evidence-based information found in the literature.

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Suggested Readings

- Alster TS, Lewis AB, Rosenbach A. Laser scar revision: comparison of CO₂ laser vaporization with and without simultaneous pulsed dye laser treatment. *Dermatol Surg.* 1998;24:1299-1302.
- Berman B, Flores F. Recurrence rates of excised keloids treated with postoperative triamcinolone acetonide injections or interferon alfa-2b injections. *J Am Acad Dermatol.* 1997;37:755.
- Fitzpatrick RE. Treatment of inflamed hypertrophic scars using intralesional 5-FU. *Dermatol Surg.* 1999;25:224-232.
- Gold MH, Foster TD, Adair MA, et al. Prevention of hypertrophic scars and keloids by the prophylactic use of topical silicone gel sheets following a surgical procedure in an office setting. *Dermatol Surg.* 2001;27(7):641-644.
- Manuskiatti W, Fitzpatrick RE. Treatment response of keloidal and hypertrophic sternotomy scars: comparison among intralesional corticosteroid, 5-fluorouracil, and 585-nm flashlamp-pumped pulsed-dye laser treatments. *Arch Dermatol.* 2002;138(9):1149-1155.
- Uebelhoer NS, Ross EV, Shumaker PR. Ablative fractional resurfacing for the treatment of traumatic scars and contractures. *Semin Cutan Med Surg.* 2012;31(2):110-120.
- Viera MH, Amini S, Valins W, Berman B. Innovative therapies in the treatment of keloids and hypertrophic scars. *J Clin Aesthet Dermatol.* 2010;3(5):20-26.
- Zouboulis CC, Blume U, Buttner P, et al. Outcomes of cryosurgery in keloids and hypertrophic scars. *Arch Dermatol.* 1993;129:1146-1151.

I. BACKGROUND Keratosis pilaris (KP) is a very common autosomal dominantly inherited disorder of follicular hyperkeratosis, affecting 50% to 80% of adolescents and about 40% of adults worldwide. KP is generally described as a skin condition of childhood and adolescence, but may worsen with puberty and pregnancy. Symptoms commonly improve with age. A questionnaire-based study reports some seasonal variation, with improved symptoms in the summer and worsening in the winter.

Several conditions associated with KP include ichthyosis follicularis, atopic dermatitis, papular atrichia, mucoepidermal dysplasia, cardiofaciocutaneous syndrome, and ectodermal dysplasia with corkscrew hairs.

II. CLINICAL PRESENTATION KP is characterized by horny folliculo-centric keratotic plugs or small papules (Figs. 26-1 and 26-2). The papules are typically acuminate, may have a surrounding erythema, and dot the otherwise normal skin on the lateral aspects of the upper arms, legs, and buttocks in a fairly regular pattern. Removal of a plug leaves a cup-shaped depression in the apex of the papule, which is soon filled by new keratotic material. The follicular bump is created by keratin accumulation and often a small coiled hair may be trapped beneath the keratin debris. KP is generally asymptomatic except for cosmetic dissatisfaction and mild pruritus. Treatment may prove challenging.

Keratosis pilaris rubra faciei is a variant of KP whereby keratotic papules are located on the face on a background of erythema. KP atrophicans or ulerythema ophryogenes (Fig. 26-3) begins in childhood, involves the cheeks and eyebrows, and is accompanied by madarosis (absence of eyelashes or eyebrows). Epidermal atrophy and perifollicular fibrosis are present. Atrophoderma vermiculata has been described as KP of the cheeks, which results in a honey-combed worm-eaten appearance resembling acne scarring.

III. WORKUP The diagnosis of KP is usually made via clinical observation without the need for further testing. A positive family history for KP can be very helpful as well. In atypical cases, a skin biopsy with histopathologic examination may be warranted to arrive at the correct diagnosis. The classic histopathology of KP shows a triad of follicular plugging, epidermal hyperkeratosis, and hypergranulosis. Sometimes a sparse perifollicular infiltrate of lymphocytes or neutrophils may also be seen. Please see Table 26-1 for other conditions that may have a similar clinical appearance.

IV. TREATMENT KP is a clinically and cosmetically troublesome disorder without a universally effective cure (Table 26-2). It is often refractory to treatment. When effective, treatment must be continuous as improvement is temporary.



Figure 26-1. Tiny perifollicular papules with central keratotic plugs on the lateral surface of the upper arm. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 26-2. More acneiform lesions of keratosis pilaris. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

Similar to eczema skin care, prevention of skin dryness with mild soaps and lubrication is recommended for nearly all cases. Emollients and keratolytics containing urea or 12% ammonium lactate (such as Amlactin and Lachydrin) may help smoothen the rough skin. Topical corticosteroids have been tried with varying success. Some patients respond to topical retinoids; however, these can easily irritate the skin of atotics, so should be started with weekly or twice-weekly



Figure 26-3. Ulerythema ophryogenes (keratosis pilaris atrophicans) involving the cheeks and eyebrows, accompanied by madarosis (absence of eyelashes or eyebrows). (Image provided by Stedman's.)

TABLE 26-1 Differential Diagnosis

Acne vulgaris
Atopic dermatitis
Darier disease (keratosis follicularis)
Erythromelanosus follicularis faciei et colli
Folliculitis
Lichen nitidus
Lichen spinulosus
Milia
Perforating folliculitis
Pityriasis rubra pilaris
Trichostasis spinulosa

applications. Severe cases may benefit from off-label use of oral retinoids. One recent study comparing tacrolimus ointment 0.1% with Aquaphor ointment found that both were effective and well tolerated. Laser therapy including long-pulsed 1064-nm Nd:YAG laser, 595-nm pulsed dye laser, or dermabrasion has shown varying improvement in KP but may not be cost effective.

TABLE 26-2	Treatment
	Emollients/lubrication and keratolytics (e.g., ammonium lactate and urea)
	Topical retinoids
	Tacrolimus ointment
	Lasers (e.g., long-pulsed 1,064-nm Nd:YAG laser and 595-nm pulsed dye laser)

Suggested Readings

Breithaupt AD, Alio A, Friedlander SF. A comparative trial comparing the efficacy of tacrolimus 0.1% ointment with Aquaphor ointment for the treatment of keratosis pilaris. *Pediatr Dermatol.* 2011;28(4):459-460.

Hwang S, Schwartz RA. Keratosis pilaris: a common follicular hyperkeratosis. *Cutis.* 2008;82(3):177-180.

Park J, Kim BJ, Kim MN, Lee CK. A pilot study of Q-switched 1064-nm Nd:YAG laser treatment in the keratosis pilaris. *Ann Dermatol.* 2011;23(3):293-298.

Poskitt L, Wilkinson JD. Natural history of keratosis pilaris. *Br J Dermatol.* 1994;130(6):711-713.

I. BACKGROUND Lentigines are benign, pigmented, persistent macules that arise from overactivity of epidermal melanocytes. Lentigines may be congenital or acquired, and there does not seem to be an increase in prevalence in a specific race or gender. A lentigo (pl. lentigines) is most often confused with a freckle. These hyperpigmented spots, which may appear at any age, are usually darker than freckles and neither increase in darkness nor fade seasonally. Histologically, lentigines have an increased number of melanocytes in the dermal-epidermal junction, increased amounts of melanin in melanocytes and basal keratinocytes, and the epidermal rete ridges are elongated and clubbed.

Solar lentigines (informally and inaccurately known as liver or age spots) appear on sun-exposed surfaces of fair-skinned people, usually in association with other changes from sun damage, including wrinkling, dryness, and actinic keratoses. The prevalence of solar lentigines increases with the age of the patient. Although these acquired lesions are induced by ultraviolet radiation, exposure to sun does not increase pigmentation. Lentiginous pigmentation has been observed following prolonged psoralen plus ultraviolet A (PUVA) therapy, although these lesions, as opposed to solar lentigines, display melanocytic cytologic atypia.

Lentigo simplex, the most common form of lentigo, may be congenital or acquired. It differs from solar lentigines in that it is not induced by sun exposure.

Mucosal lentigines are variants of simple lentigines that are located on mucosal surfaces. They may occur on the lips, vulva, and penis. Labial melanotic macules occur most commonly on the lower lip of young women.

Multiple lentigines may be associated with various disorders such as Peutz-Jeghers syndrome (PJS), Moynahan syndrome, Addison disease, or others associated with increases in adrenocorticotrophic hormone.

II. CLINICAL PRESENTATION Lentigo simplex is a 1- to 5-mm brown macule that can be found on any cutaneous surface. They do not necessarily have predilection for sun-exposed sites. They are well-circumscribed round/oval uniformly brown or brownish-black macules. These lesions may appear at birth, during infancy, or during adulthood.

Solar lentigines, on the other hand, are pale to dark-brown macules found on sun-exposed areas, especially the dorsum of the hand and face. They vary in color and size (Figs. 27-1 and 27-2).

Multiple lentigines, especially if present on the palms, soles, mucous membranes, or non-sun-exposed skin, are often indicative of systemic disorders with significant internal abnormalities. Examples of such associations are the PJS (lentigines, intestinal polyposis, and ovarian tumors), the LEOPARD syndrome (lentigines, ECG changes, ocular hypertelorism, pulmonic stenosis,



Figure 27-1. Solar lentigo on dorsal hand. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 27-2. Flat, brown patch, characteristic of lentigo. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

abnormal genitalia, retardation, and deafness), and the LAMB syndrome (lentigines, atrial myxoma, mucocutaneous myxomas, and blue nevi). In PJS, lentigines are present on the lips or oral mucosa for most patients, while other locations may be affected as well. A total of 95% of cases show characteristic

skin findings in PJS. In LEOPARD syndrome, lentigines occur on both sun-exposed and sun-protected sites. Lastly, in LAMB syndrome, lentigines may appear on the lips and genital areas in early childhood.

III. WORKUP It is useful to examine pigmented lesions under Wood’s light to define margins of lentigo simplex. When pigment is present in the epidermis, the contrast between normal and hyperpigmented skin is enhanced. When pigment is present in the dermis, the contrast is not enhanced compared with ambient visible light. Patients with generalized lentigines deserve a thorough history and physical examination to search for related systemic findings. For example, the presence of multiple lentigines at a young age should raise suspicion for autosomal dominant disorders, especially PJS or Moynahan syndrome. Please refer to the differential diagnoses (Table 27-1) for other conditions that appear similar to lentigines.

IV. TREATMENT Benign lentigines do not need to be treated. If patients request cosmetic removal, multiple treatment options are available. As with many other skin conditions, sun protection should be emphasized as part of the treatment and prophylaxis. Before treating these patients, however, careful evaluation is warranted to first definitively rule out lentigo maligna or melanoma. Multiple case series describe patients who were referred for laser treatment of “lentigines” and were found to have malignant lesions.

A. Cryosurgery. Hyperpigmented macules and patches may be removed or their intensity of pigmentation diminished by light cryosurgical freezing (5 to 7 seconds of intermittent freeze) with liquid nitrogen. Melanocytes

TABLE 27-1 Differential Diagnosis of Lentigines	
Differential Diagnosis of Lentigo Simplex	
<ul style="list-style-type: none">• Ephelides• Junctional nevomelanocytic nevus• Atypical melanocytic nevus• Café-au-lait macule• Lentigo maligna/melanoma	
Differential Diagnosis of Solar Lentigo	
<ul style="list-style-type: none">• Lentigo simplex• Ephelides• Junctional nevomelanocytic nevus• “Reticulated” seborrheic keratoses• Pigmented actinic keratoses• Lentigo maligna/melanoma	

are more sensitive to cold injury than keratinocytes and may be selectively damaged by this technique. However, lesions may recur after therapy.

- B. Laser/Light Therapy.** Treatment with the Q-switched ruby, Q-switched alexandrite, and Q-switched Nd:YAG lasers is effective. Lasers with longer pulse widths (milliseconds), such as long-pulse Nd:YAG or pulsed dye laser (PDL), may also be helpful. These lasers all target melanocytes and decrease hyperpigmentation, leaving the surrounding skin undamaged. However, use of lasers still carries a small risk of dyschromia and scarring. PDL and intense pulsed light (IPL) handpieces usually offer larger spot sizes, making them useful for treating large areas.

C. Topical Bleaching Agents

- 1. Hydroquinone (HQ) Alone.** The intensity of pigmentation in lentiginos may be decreased by the regular application of 2% to 5% HQ cream or lotion twice daily for weeks to months. The concentration of over-the-counter HQ products is usually 2%. Dermatologists commonly prescribe a 4% concentration although pharmacists can mix concentrations up to 10%. HQ acts by (i) competing with tyrosine oxidation by acting as an alternate substrate for tyrosinase, the enzyme that converts tyrosine to melanin and (ii) selectively damaging melanosomes and melanocytes. About 4- to 6-week monotherapy is required before hypopigmenting effects are seen. The most common side effects are skin irritation and contact dermatitis. A rare side effect of extended use of HQ is the development of exogenous ochronosis that is extremely difficult to reverse. Alternating HQ in 4-month cycles with other depigmenting agents can prevent or reduce side effects.
- 2. Retinoids** have been established as an important class of drugs for treating many pigmentary disorders. A review in 2009 found evidence to support the effectiveness of topical tretinoin in treating both melasma and solar lentiginos as a monotherapy or combination therapy. Possible side effects are erythema, scaling, or rare allergic contact dermatitis. Retinoid dermatitis can induce postinflammatory hyperpigmentation. If patients are unable to tolerate tretinoin gel or cream, less irritating tretinoin gel with microspheres or adapalene gel may be used.
- 3. Mequinol (4-Hydroxyanisole)** is a substrate of the enzyme tyrosinase and acts as a competitive inhibitor of melanogenesis. The combination of mequinol 2% and tretinoin 0.01% is available as Solage and is indicated for twice-daily dosing.
- 4. Other Treatments** advocated for the treatment of hyperpigmentation include topical azelaic acid, kojic acid, glycolic acid (either in topical preparations or peels in concentrations of 30% to 70%), topical Jessner solution, and microdermabrasion.
- 5. Combination Therapy.** Numerous formulations are available on the market combining HQ together with sunscreens, vitamins, and α -hydroxy acids. Topical HQ and retinoids have been established as effective treatment combination for hyperpigmented, photoaging skin. For example, a commonly prescribed prepackaged version of the original Klignan formula is Triluma cream. This compound is a mixture of three ingredients including 4% HQ, tretinoin 0.05%, and flucinolone acetonide 0.01%, which proved to be an effective combination therapy.

D. Combinations of In-Office Procedures and Maintenance Topical Therapies have been shown to give greater efficacy than using either treatment by itself. In-office chemical peels plus maintenance topical HQ and retinoids have shown high patient satisfaction in a recent case series.¹

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REFERENCE

1. Cohen JL, Makino E, Sonti S, et al. Synergistic combination of an in office procedure and home regimen for the treatment of facial hyperpigmentation. *J Clin Aesthet Dermatol*. 2012;5(4):33-35.

Suggested Readings

- Cook-Bolden FE, Hamilton SF. An open-label study of the efficacy and tolerability of microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants for the treatment of hyperpigmentation. *Cutis*. 2008;81(4):365-371.
- Kang HY, Valerio L, Bahadoran P, et al. The role of topical retinoids in the treatment of pigmentary disorders: an evidence-based review. *Am J Clin Dermatol*. 2009;10(4):251-260.
- Konishi N, Kawada A, Kawara S, et al. Clinical effectiveness of a novel intense pulsed light source on facial pigmentary lesions. *Arch Dermatol Res*. 2008;300:S65-S67.
- Sardesai VR, Kolte JN, Srinivas BN. A clinical study of melisma and a comparison of the therapeutic effect of certain currently available topical modalities for its treatment. *Indian J Dermatol*. 2013;58(3):239.
- Sasaya H, Kawada A, Wada T, et al. Clinical effectiveness of intense pulsed light therapy for solar lentigines of the hands. *Dermatol Ther*. 2011;24(6):584-586.
- Stankiewicz K, Chuang G, Avram M. Lentigines, laser, and melanoma: a case series and discussion. *Lasers Surg Med*. 2012;44(2):112-116.
- Trelles MA, Valez M, Gold MH. The treatment of melasma with topical creams alone, CO₂ fractional ablative resurfacing alone, or a combination of the two: a comparative study. *J Drugs Dermatol*. 2010;9(4):315-322.

I. BACKGROUND Melasma is a common acquired and chronic disorder of hyperpigmentation affecting up to 5 million Americans. It most often involves the face and women are more frequently affected than men. Those of African, Asian, or Hispanic descent with Fitzpatrick skin type III or greater are at higher risk for this condition. Melasma can negatively affect quality of life, especially in patients with lesser amounts of education and underlying psychological disease.

The pathogenesis of melasma is poorly understood but it is likely multifactorial and due to a combination of environmental exposures, hormones, and cellular factors such as cytokines. Ultraviolet (UV) light is an important inducer of melasma, evident by the fact that this condition occurs in sun-exposed sites and worsens with further exposure. Histopathologic evaluation shows larger and more prominently dendritic melanocytes rather than an increased density of these cells. Historically, this condition has also been strongly associated with increased levels of estrogen and progesterone and its onset is often reported during pregnancy and while taking oral contraceptives. Unfortunately, this relationship remains unclear and circulating levels of hormones do not correlate with the presence and severity of melasma.

II. CLINICAL PRESENTATION Melasma most often occurs in young to middle-aged women with a prevalence that increases with age. It is characterized by symmetric, light to dark, or gray-brown patches with well-defined borders. Lesions may range from 0.5 cm to greater than 10 cm in diameter. The three categories of melasma localization include centrofacial, malar, and mandibular. The centrofacial type is most common with patches located at the forehead, cheeks, nose, upper lip, and chin (Figs. 28-1 and 28-2). The malar type is more limited with disease at the nose and cheeks, and, in mandibular disease, involvement is usually at bilateral rami. The condition has also been reported at the forearms and chest but this is less well described (Fig. 28-3).

When the disease first appears during pregnancy, it often resolves after childbirth, though this may be less frequent in women of darker skin types. When occurring in the context of an oral contraceptive, melasma often becomes more chronic in nature and can persist for years.

III. WORKUP Most often, melasma can be diagnosed by history and physical examination alone. However, examination by Wood lamp may better characterize the condition, which has classically been described based on whether pigment appears to be epidermal, dermal, mixed, or indeterminate. Epidermal patches should be accentuated and dermal patches should become less obvious when exposed to the lamp. Traditionally, dermal disease has been considered



Figure 28-1. Melasma of the cheeks. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 28-2. Melasma of the upper cutaneous lip. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

more difficult to treat. However, recent studies suggest that even in melasma that seems epidermal by Wood lamp examination, dermal melanin deposition is common. This may explain why the condition is oftentimes challenging to treat regardless of Wood lamp results.

At times the differential diagnosis may include postinflammatory hyperpigmentation, solar lentigines, ephelides, drug-induced pigmentation,



Figure 28-3. A less common presentation of melasma at the forearm. (Image provided by Stedman's.)

actinic lichen planus, lichen planus pigmentosus, facial acanthosis nigricans, frictional melanoses, exogenous ochronosis, erythema dyschromicum perstans, poikiloderma of Civatte, and bilateral acquired nevus of Ota-like macules (Hori nevus) (Table 28-1). When the diagnosis is unclear, biopsy may prove enlightening or rule out other disorders.

Some reports have linked the presence of melasma to underlying thyroid disease. If clinical suspicion is elevated due to a positive review of systems, a screening thyroid-stimulating hormone may be prudent.

IV. TREATMENT Melasma can be a difficult condition to treat and is appropriately approached with a combination of modalities. Photoprotection and topical depigmenting agents are mainstays (Table 28-2); camouflage makeup can also be useful. Chemical peels and laser and light interventions are more aggressive forms of management with higher side-effect profiles.

A. Photoprotection. This should be employed daily in the form of sunscreen as well as photoprotective clothing and hats and sun avoidance. Though sunscreens have yet to be studied as a solitary melasma therapy, based on clinical experience, dermatologists consider their use to be imperative. Sunscreens likely enhance the efficacy of other melasma treatments and can also be a successful preventive measure. Patients should be instructed to use a UVA- and UVB-protective sunscreen with SPF 30 or higher. Products

TABLE 28-1 **Differential Diagnosis**

- Actinic lichen planus
- Bilateral acquired nevus of Ota-like macules (Hori nevus)
- Drug-induced hyperpigmentation
- Erythema dischromicum perstans
- Exogenous ochronosis
- Facial acanthosis nigricans
- Frictional melanoses
- Lichen planus pigmentosus
- Poikiloderma of Civatte
- Postinflammatory hyperpigmentation
- Solar lentigines

TABLE 28-2 **Primary Treatment Options**

1. Photoprotection with broad-spectrum sunscreen
2. Topical hydroquinone 2–4%
3. Triple combination therapy with topical hydroquinone, tretinoin, and a corticosteroid

that include physical blockers such as zinc oxide and titanium dioxide are particularly helpful and reapplication is recommended every 2 hours.

- B. Hydroquinone.** This is likely the single most effective depigmenting agent available and is thought to work by inhibiting tyrosinase. Ennes and colleagues showed in a double-blinded, placebo-controlled trial of 48 melasma patients that hydroquinone 4% led to total improvement in 38% of patients versus 8% of patients receiving placebo. It is manufactured in strengths between 2% and 5% with a 2% formulation available over the counter. Stronger prescription doses (most commonly 4%) are more effective as well as more irritating. Application is twice daily to affected sites, but can be decreased to once daily in the setting of irritation. The recommended length of treatment varies but improvement may be noticed after 5 to 7 weeks and treatment may be continued for 3 to 12 months. Patients should be informed of possible side effects, including irritant contact dermatitis, postinflammatory hyperpigmentation, and exogenous ochronosis. The latter may be related to the presence of higher over-the-counter concentrations (up to 8%) in other countries. The medication is considered a safe option by most experts.

- C. Combination Therapy.** Multiple dual and triple combination therapies have been used to treat melasma, but the most effective include topical hydroquinone, a topical retinoid, and a topical steroid. In 1975, Kligman and Willis reported one of the first successful formulas consisting of hydroquinone 5%, tretinoin 0.1%, and dexamethasone 0.1%. In more recent years, a very popular preparation has included hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%. Triple therapy cream may lead to complete clearance in a quarter of patients after 8 weeks. The product is applied at night and daily sunscreen is an important adjunct. This combination product is not currently available commercially. Some pharmacies are able to compound the individual agents to create a triple therapy cream, and the components can be prescribed separately. Negative aspects of this therapy include its high price, skin irritation, and risk of steroid atrophy.
- D. Other Topical Bleaching Creams.** Other creams may be considered as adjunctive agents or even primary treatments due to their decreased cost. They include azelaic acid, kojic acid, ascorbic acid, arbutin and deoxyarbutin, licorice extract, ellagic acid, rucinol, and soy. The more commonly used entities are described below.
- 1. Azelaic Acid** is a 9-carbon dicarboxylic acid derived from *Pityrosporum ovale*, which shows a weak reversible competitive inhibition of tyrosinase. It is available with a prescription as a 20% cream or a 15% gel and is applied twice daily for 3 to 12 months and well tolerated. If there is no improvement in 3 months, other measures should be considered. Azelaic acid may be more effective when used in combination with tretinoin 0.05% or 0.1% cream.
 - 2. Kojic Acid** is produced by *Aspergillus oryzae* and *Penicillium* species and inhibits tyrosinase by chelating copper at the enzyme's active site. It is available over the counter in 2% preparations and may be applied daily. Improvement is usually noticeable in 3 months if the therapy is to be effective. Important to keep in mind is that kojic acid is a sensitizer and may cause irritation.
 - 3. Ascorbic Acid (Vitamin C)** can be obtained in cream form and is also thought to work by interacting with copper at the active site of tyrosinase. It is available in over-the-counter preparations between 10% and 20% but has limited supporting data. Vitamin C iontophoresis has also shown limited efficacy.
- E. Camouflage.** Given that many melasma treatments improve but do not resolve the condition, makeup is often an important adjunctive measure. Specialized products include Dermablend (Vichy Laboratories, Paris, France), Covermark/CM Beauty (CM Beauty, Northvale, NJ), and Cover FX (Cover FX Skin Care, Toronto, Ontario, Canada). They are available in a variety of shades.
- F. Chemical Peels.** α -Hydroxy acid peels, particularly those including glycolic acid ranging from 10% to 70%, may lead to some improvement of melasma. Other peels that have been studied include tretinoin 1% to 5%, Jessner solution (salicylic acid, lactic acid, resorcinol, and ethanol), 10% to 50% trichloroacetic acid, lactic acid, and salicylic acid 20% to 30%. Many trials describe peels used at 2- to 4-week intervals for up to 12 treatments, and they are likely more effective when used in combination with topical

therapies such as hydroquinone. Providers should keep in mind that data are somewhat limited regarding the effectiveness of peels and relapse may occur. When considering a peel for adjunctive therapy, patients should be counseled regarding the risk of irritation and subsequent postinflammatory hyperpigmentation, particularly if they possess darker skin types.

G. Laser and Light. Devices are considered to be third-line therapeutic options in those patients with recalcitrant melasma. They are more effective when used as an adjunct to topical treatment with hydroquinone or triple combination therapy. Specifically, 4 to 8 weeks of pretreatment with a bleaching agent prior to a laser procedure may be quite helpful. Importantly, physicians should be aware that the risks of postinflammatory hyperpigmentation, hypopigmentation, and erythema are substantial.

Fractional resurfacing is one of the best supported laser interventions and is Food and Drug Administration approved for melasma. In 2005, an early pilot study described 10 women who received four to six treatments with a fractionated 1,550-nm laser. Six subjects demonstrated 75% to 100% clearance and only one patient developed postinflammatory hyperpigmentation. A device that employs both 1,550- and 1,927-nm wavelengths is similarly effective. One of the most recent advances in the management of melasma includes combination therapy with microdermabrasion followed by immediate treatment with the Q-switched neodymium-doped yttrium–aluminum–garnet (Nd:YAG) laser at low fluences. Kauvar used this intervention in combination with photoprotection and hydroquinone and showed that all of 27 patients demonstrated at least 50% improvement in melasma appearance and 80% showed a >76% improvement after up to four treatments. Side effects were limited to postprocedural erythema and 80% of patients maintained clearance for up to 12 months. Other devices with reported efficacy in melasma treatment include intense pulsed light, pulsed CO₂ (10,600-nm) laser used in conjunction with the Q-switched alexandrite (755-nm) laser, and the Q-switched erbium:yttrium–aluminum–garnet laser.

Suggested Readings

- Ennes SBP, Paschoalick RC, Mota De Avelar Alchorne M. A double-blind, comparative, placebo-controlled study of the efficacy and tolerability of 4% hydroquinone as a depigmenting agent in melasma. *J Dermatol Treatment*. 2000;11(3):173-179.
- Grimes PE. Melasma: etiologic and therapeutic considerations. *Arch Dermatol*. 1995;131(12):1452-1457.
- Kauvar ANB. The evolution of melasma therapy: targeting melanosomes using low-fluence Q-switched neodymium-doped yttrium aluminum garnet lasers. *Semin Cutan Med Surg*. 2012;31(2):126-132.
- Kligman AM, Willis I. A new formula for depigmenting human skin. *Arch Dermatol*. 1975;111(1):40-48.
- Rokhsar CK, Fitzpatrick RE. The treatment of melasma with fractional photothermolysis: a pilot study. *Dermatol Surg*. 2005;31(12):1645-1650.
- Sheth VM, Pandya AG. Melasma: a comprehensive update: part I. *J Am Acad Dermatol*. 2011;65(4):689-697.
- Sheth VM, Pandya AG. Melasma: a comprehensive update: part II. *J Am Acad Dermatol*. 2011;65(4):699-714.

I. BACKGROUND Milia are benign, asymptomatic, small, subepidermal, keratinous cysts found in individuals of all ages, most often on the face (Figs. 29-1 to 29-3). Milia appear as tiny (1 to 2 mm), white, raised, round lesions covered by a thinned epidermis found primarily on the cheeks and eyelids. No orifice can be seen. Some cases of idiopathic calcinosis cutis and syringomas may clinically mimic milia.

II. CLINICAL PRESENTATION Primary milia are noninflammatory collections of lamellated keratin most frequently found within the undifferentiated sebaceous cells that surround vellus hair follicles. Milia found in infants tend to disappear spontaneously in a few months, but lesions in adults can be chronic. Most arise spontaneously, but others may be localized in areas of damaged skin associated with bullous disease such as porphyria cutanea tarda, bullous lupus erythematosus, and epidermolysis bullosa. Milia may also arise in areas treated by dermabrasion, laser resurfacing, and, rarely, at the site of radiation therapy. These secondary milia arise predominantly from eccrine duct epithelium.

Eruptive milia are referred to as the sudden appearance of multiple lesions. Milia and plaque are a rare and uncommon variant of primary milia. This manifestation of milia is characterized by numerous small milia that are grouped overlying an erythematous plaque.

III. WORKUP Inquire about previous inflammatory or blistering skin disease, trauma, use of occlusive cosmetic products, or photosensitivity. A short course of treatment with clobetasol ointment has been implicated in the formation of milia. If a large number of milia arise in a young patient, it may be pertinent to ask about affected relatives in order to rule out Loeys-Dietz syndrome, which is associated with arterial disease and eruptive milia.

IV. TREATMENT

A. Milia are easily removed without anesthesia as follows:

1. Gently incise the thin epidermis covering the milium with a no. 11 scalpel blade.
2. Carefully sever and tease away any connection or adhesions between the cyst and the overlying skin.
3. Apply mild pressure with a comedo extractor, curette, tongue blade, two cotton-tipped applicators, or the dull edge of the scalpel blade. The small keratin kernel should pop out as an intact ball.



Figure 29-1. Milia. Some of the larger lesions are cystic. (From O'Doherty N. *Atlas of the Newborn*. Philadelphia, PA: JB Lippincott; 1979:33.)

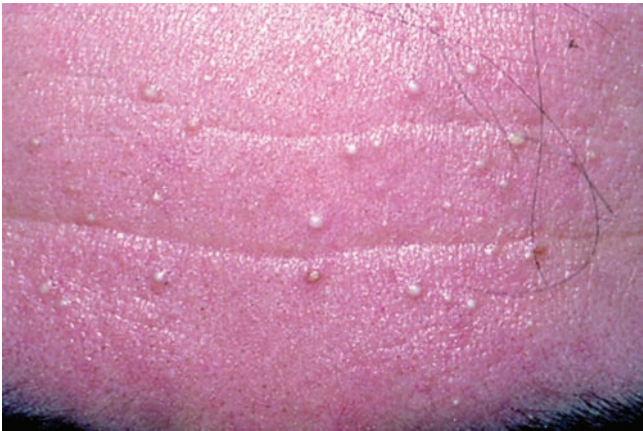


Figure 29-2. Milia. These epidermal cysts contain keratin. They are 1 to 2 mm in diameter and are white to yellow. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

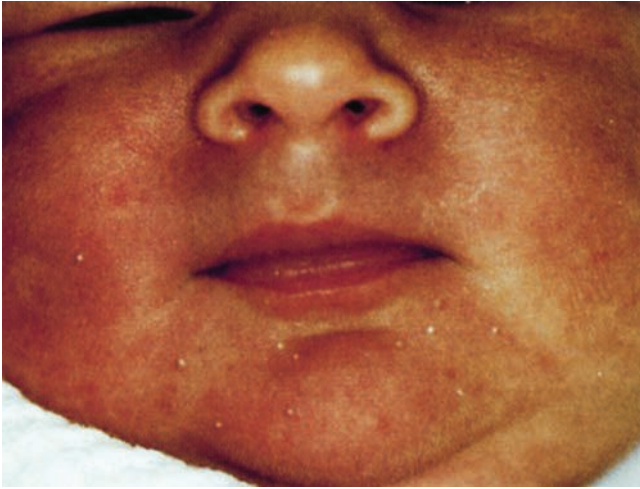


Figure 29-3. Milia. (Used with permission from Fletcher MA. *Physical Diagnosis in Neonatology*. Philadelphia, PA: Lippincott Williams & Wilkins; 1998:124.)

- B. A Sterile Hypodermic Needle** may be used to enucleate the milium.
- C. Light Electrodesiccation** with a fine needle is also effective.
- D. Topical Agents** such as retinoic acid, retinol, or α -hydroxy acids may be useful adjuvant therapy to prevent the formation of new milia.

ACKNOWLEDGMENT

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Suggested Readings

- Berk DR, Bayliss SJ. Milia: a review and classification. *J Am Acad Dermatol*. 2008;59(6): 1050-1063.
- Dogra S, Kanwar AJ. Milia en plaque. *J Eur Acad Dermatol Venerol*. 2005; 9:263-264.
- Lloyd BM, Braverman AC, Anadkat MJ. Multiple facial milia in patients with Loeys-Dietz syndrome. *Arch Dermatol*. 2011;147(2):223-226.
- Stefanidou MP, Panayotides JG, Tosca AD. Milia en plaque: a case report and review of the literature. *Dermatol Surg*. 2002;28:291-295.

I. BACKGROUND Molluscum contagiosum (MC) is a common, self-limited viral lesion caused by four closely related subtypes of a DNA-containing poxvirus. Infection occurs worldwide, with viral subtypes varying geographically. In the United States, molluscum contagiosum virus subtype 1 (MCV-1) accounts for 90% of all cases. In the setting of HIV, however, MCV-2 is implicated in approximately 60% of infections.

Viral infection is contracted through skin-to-skin contact, fomite transmission, and autoinoculation. Once exposed, MCV replicates in the cytoplasm of infected keratinocytes. Viral particles may be seen in all epidermal layers, although replication is postulated to occur in the more differentiated cell layers. MCV contains many novel genes, including the IL-18-binding protein gene, that are effective in blocking host immune defenses and enabling viral particle survival and spread.

MCV peak incidence is among children younger than 5 years of age, with a reported lifetime prevalence of up to 25% in some studies. Widespread MC can occur in patients with atopic dermatitis, leukemia, sarcoidosis, and immunosuppressed states, like AIDS.

II. CLINICAL PRESENTATION MC lesions are discrete, skin-colored or pearly white, raised, waxy-appearing firm papules 1 to 5 mm in diameter with a central punctate umbilication (Fig. 30-1). MC most commonly occurs on the trunk, thighs, and skin folds. Involvement of the palms and soles is rare. Sexually transmitted MC involves the lower abdomen, groin, genitals, and proximal thigh areas. Widespread, disfiguring lesions can be seen in the setting of immune compromise, as in AIDS. Especially in children with MC in the setting of atopic dermatitis, skin irritation with erythema, scale, and pruritus around MC lesions is common and signifies the development of a host immune response to the virus (Fig. 30-2).

III. WORKUP Diagnosis is generally made by clinical assessment. However, when necessary, etiology may be confirmed with microscopic or histopathologic examination. A lesion can be incised, smeared between two glass slides, and stained (with Wright, Giemsa, or Gram stain). Using this in-office technique, or obtaining tissue biopsy for hematoxylin and eosin preparation, light microscopy demonstrates keratinocytes that contain eosinophilic cytoplasmic inclusion bodies also known as Henderson-Patterson or molluscum bodies. These inclusion bodies, consisting of virions in various stages of development, push the host cell to the periphery, giving the appearance of a signet ring cell.

In children with MC, no routine laboratory studies are indicated. However, sexually active adolescents and adults with MC should be screened for the



Figure 30-1. Molluscum contagiosum. Dome-shaped, pink papules with central umbilication. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 30-2. Molluscum contagiosum. Characteristic lesions, many excoeriated, in the setting of atopic dermatitis of the flexural creases. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

presence of other coexisting sexually transmitted diseases, including HIV, and other sources of immune compromise.

IV. TREATMENT Because MC generally remits spontaneously in children, reassurance and clinical monitoring may be sufficient in some cases. Strong evidence of the efficacy of most forms of treatment is lacking, and observation remains the preferred treatment of many, as intervention may be painful and lead to scarring. Currently, no Food and Drug Administration (FDA)-approved

medications exist for the treatment of MC. On the other hand, treatment can achieve a rapid clinical response and serves to minimize autoinoculation and transmission to other individuals, but therapy must be weighed against the risks of short-term dyspigmentation and long-term scarring. The clinician must discuss the benefit and risk of treatment honestly with the child and the parents. Multiple treatments may be necessary, and, following each treatment, the patient should have repeat examinations at 2- to 4-week intervals (Table 30-1).

- A. Curettage.** Many clinicians prefer lesion curettage under local anesthesia, as lesions may be removed immediately. Data on its efficacy, however, remain mixed. One study comparing the efficacy of curettage to cantharidin, salicylic and glycolic acid, and imiquimod in children and adolescents found an 80% clearance with curettage after the first treatment visit, while reporting much lower clearance and much higher rates of side effects in the other treatment modalities.¹
- B. Cryotherapy.** Liquid nitrogen application directly to the lesion, either by spraying or by cotton tip application for 6 to 10 seconds, is another rapid treatment modality. Although treatment is well tolerated by most patients, the pain associated with application can be a limiting factor in children when multiple lesions are present.
- C. Podophyllotoxin.** The efficacy of podophyllotoxin, an antimitotic agent, was demonstrated in a randomized trial of 150 males aged 10 to 26 years, who had MC in the thighs or genital areas. Study patients applied either 0.5% or 0.3% podophyllotoxin cream, while the control group applied placebo. After twice-daily applications for 3 consecutive days in a week (with 4-day breaks) for up to 4 weeks, the rates of clearance for the 0.5%, 0.3%, and placebo groups at the study's end were 92%, 52%, and 16%, respectively.²
- D. Cantharidin.** Cantharidin, a topical blistering agent derived from the Coleoptera beetle, may be painted directly onto each lesion using the blunt end of a cotton swab. The lesions are covered and then washed with

TABLE 30-1 Treatment Options for Molluscum Contagiosum

- Physical ablation
 - Curettage
 - Cryotherapy
- Cytotoxic agents
 - Podophyllotoxin, topical
 - Cantharidin, topical
- Immunomodulatory agents
 - Imiquimod, topical
- Other
 - Cimetidine, oral
 - Topical retinoids

soap and water 2 to 6 hours after application or with onset of blistering. Cantharidin induces a small blister at the treatment site after direct application. MC lesions disappear as the blister heals. The lesion usually heals without scarring, but treatment may leave pigmentary changes. In a study of 300 children treated with cantharidin, 90% of patients experienced full clearing, with the average number of clinic appointments being 2.1. No major side effects were reported, and 95% of parents reported that they would choose cantharidin again to treat their child's MC.³ However, caution must be advised with cantharidin, due to the risk of dyspigmentation and possible scarring, and treatment typically avoided for facial lesions.

- E. Topical Retinoids.** Topical adapalene, tretinoin, and tazarotene treat MC through stimulating local irritation, which serves to damage the viral protein-lipid membrane. While numerous case reports suggest its success, there is a lack of randomized control trials evaluating efficacy.
- F. Imiquimod.** Originally approved by the FDA for the treatment of genital warts, topical imiquimod therapy is an immune response modifier that activates Toll-like receptor 7, while inducing secretion of interferon- α and other cytokines thought to assist in stimulating an immunologic response to MCV. Imiquimod is applied to the lesional skin at least three times per week and is left on the skin for 6 to 10 hours prior to rinsing. In one open-label study, seven children and eight adults with MC (three with HIV) self-administered 5% imiquimod cream daily, 5 days/week for 4 to 16 weeks. Eighty percent of the patients experienced either complete clearance or a >50% reduction in lesion size.⁴
- G. Cimetidine.** Dohil and Prendiville showed full clearance of lesions in 9 of 13 pediatric patients after receiving 40 mg/kg/day of cimetidine (Tagamet) for 2 months. Caution is advised because cimetidine interacts with many other systemic medications.⁵

REFERENCES

1. Hanna D, Hatami A, Powell J, et al. A prospective randomized trial comparing the efficacy and adverse effects of four recognized treatments of molluscum contagiosum in children. *Pediatric Dermatol.* 2006;23:574.
2. Syed TA, Lundin S, Ahmad M. Topical 0.3% and 0.5% podophyllotoxin cream for self-treatment of molluscum contagiosum in males. A placebo-controlled, double-blind study. *Dermatology.* 1994;189:65.
3. Silverberg NB, Sidbury R, Mancini AJ. Childhood molluscum contagiosum: experience with cantharidin therapy in 300 patients. *J Am Acad Dermatol.* 2000;43:503.
4. Hengge UR, Esser S, Schultewalter T, et al. Self-administered topical 5% imiquimod for the treatment of common warts and molluscum contagiosum. *Br J Dermatol.* 2000;143:1026-1031.
5. Dohil M, Prendiville JS. Treatment of molluscum contagiosum with oral cimetidine: clinical experience on 13 patients. *Pediatr Dermatol.* 1996;13:310-312.

Suggested Readings

- Dohil MA, Lin P, Lee J, Lucky AW, Paller AS, Eichenfield LF. The epidemiology of molluscum contagiosum in children. *J Am Acad Dermatol.* 2006;54:47-54.
- Myskowski PL. Molluscum contagiosum: new insights, new directions. *Arch Dermatol.* 1997;133:1039-1041.

I. BACKGROUND Perioral (periorificial) dermatitis is a distinct clinical entity that can easily be confused with rosacea, seborrheic dermatitis, eczematous dermatitis, or acne. It primarily affects young women and is usually found around the mouth (Figs. 31-1 and 31-2) but occasionally around the nose or eyes. Pediatric cases are more common in boys. The underlying cause is unclear. *Candida*, *Demodex*, fluorinated toothpastes, chapping, irritation, and oral contraceptives have been implicated. As with rosacea, prolonged use of potent topical or inhaled corticosteroids can cause an eruption with similar features and can perpetuate preexisting disease.

Perioral (periorificial) dermatitis is found at a significantly increased rate in atopic individuals. Compared with patients with rosacea, those with perioral dermatitis have significantly increased transepidermal water loss and atopic diathesis.

II. CLINICAL PRESENTATION Although often described as a variant of rosacea, perioral (periorificial) dermatitis is distinct. It may be distinguished by the absence of flushing or telangiectasias, the morphology and distribution of the papules, and its incidence in the pediatric population.

Discrete erythematous or flesh-colored papules and papulopustules are seen singly, in clusters, or in confluent plaques around the mouth, sparing of a 3- to 5-mm zone below the vermilion border. Lesions may occasionally occur around the nose and on the malar areas below and lateral to the eyes. Pediatric patients particularly may have periocular and perinasal papules. In 10% to 20% of patients, the disease will extend to the glabella and the periocular region. There is often a persistent erythema of the nasolabial folds that may extend around the mouth and onto the chin. Long-standing lesions show a flatter, more confluent eruption, with superimposed dry scaling. The differential diagnosis includes seborrheic dermatitis, acne, rosacea, contact or irritant dermatitis, nutritional deficiencies, or the rare glucagonoma syndrome (Table 31-1).

III. WORKUP The diagnosis of perioral dermatitis is usually made with clinical observation. No specific laboratory testing is indicated. Skin biopsy is rarely needed, but would most commonly demonstrate similar findings to rosacea.

IV. TREATMENT Withdrawal of topical corticosteroids, if applicable, is the first step. Patients should be informed that they may initially flare after withdrawal, but this will be temporary (Table 31-2).

A. Systemic Therapy. Systemic tetracyclines such as doxycycline or minocycline are a reliable first-line therapy. Dosing can vary depending on the variety of available preparations and the patient. Both anti-inflammatory



Figure 31-1. Perioral dermatitis. Erythematous papules on the chin and cheeks. Notice the characteristic sparing of the lip adjacent to the vermilion border as well as the melolabial folds. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 31-2. Perioral dermatitis due to topical steroid use. (Image provided by Stedman's.)

and antimicrobial dosing levels may be effective depending on severity of flare. Tetracyclines are contraindicated in children younger than 8 years and oral erythromycin is an accepted treatment.

- B. Topical Therapy.** Topical therapy with antibiotics including tetracyclines, erythromycin, clindamycin, sulfur-based products, and metronidazole has

TABLE 31-1 Differential Diagnosis

- Seborrheic dermatitis
- Acne vulgaris
- Rosacea
- Contact irritant or allergic dermatitis
- Nutritional deficiencies
- Glucagonoma syndrome (rare)

TABLE 31-2 Primary Treatment Options

1. Topical antibiotics
 - a. Metronidazole
 - b. Clindamycin
2. Oral antibiotics (tetracycline family)
 - a. Doxycycline
 - b. Minocycline
3. Topical calcineurin inhibitors
 - a. Pimecrolimus
 - b. Tacrolimus

demonstrated efficacy. **Topical calcineurin inhibitors** such as pimecrolimus 1% cream or tacrolimus twice daily have demonstrated benefit. **Topical retinoids** including adapalene have shown efficacy in some patients, although they may initially cause dryness and irritation. **Azelaic acid 20%** cream applied twice daily has been helpful in clearing perioral dermatitis. **Nonfluorinated corticosteroid** cream may be of symptomatic benefit and can be helpful in the transition from higher potency topical steroid abuse to topical or oral antibiotic therapy but will not cure the eruption. Fluorinated corticosteroids must be avoided assiduously.

- C. Photodynamic Therapy (PDT).** PDT with 5-ALA and blue light activation weekly for 4 weeks was shown to be effective when compared to topical clindamycin.

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Suggested Readings

- Antille C, Saurat JH, Lubbe J. Induction of rosaceiform dermatitis during treatment of facial inflammatory dermatoses with tacrolimus ointment. *Arch Dermatol*. 2004;140:456-460.
- Dirschka T, Szliska C, Jackowski J, et al. Impaired skin barrier and atopic diathesis in perioral dermatitis. *J Dtsch Dermatol Ges*. 2003;1:199.
- Jansen T. Azelaic acid as a new treatment for perioral dermatitis: results from an open study. *Br J Dermatol*. 2004;151:933-934.
- Lipozencic J, Ljubojevic S. Perioral dermatitis. *Clin Dermatol*. 2001;29:157-161.
- Oppel T, Pavicic T, Kamann S, Bräutigam M, Wollenberg A. Pimecrolimus cream 1% efficacy in perioral dermatitis—results of a randomized, double-blind, vehicle-controlled study in 40 patients. *J Eur Acad Dermatol Venereol*. 2007;21:1175-1180.
- Richey DF, Hopson B. Photodynamic therapy for perioral dermatitis. *J Drugs Dermatol*. 2006;5(2 Suppl):12-16.
- Wolf JE, Kerrouche N, Arsonnaud S. Efficacy and safety of once-daily metronidazole 1% gel compared with twice-daily azelaic acid 15% gel in the treatment of rosacea. *Cutis*. 2006;77:3-11.

Perlèche (Angular Cheilitis)

Allison L. Goddard

- I. BACKGROUND** Angular cheilitis (also known as perlèche, cheilosis, or angular stomatitis) is a chronic inflammatory condition located at the labial commissures (corner of the mouth) (Fig. 32-1). It is felt to be a reaction pattern to one or more causes, including superimposed infection, nutritional deficiencies, or mechanical disturbances. Infectious agents are most commonly *Candida albicans* and, to a lesser degree, streptococci or staphylococci. Nutritional deficiencies may include riboflavin or zinc and angular cheilitis may be the presenting sign of anorexia nervosa or bulimia. In edentulous patients, overclosure of the jaws will lead to tissue folds that create a chronically moist environment. Trauma from dental flossing, lip licking, and drooling may also contribute.
- II. CLINICAL PRESENTATION** Angular cheilitis presents with erythematous fissures, crusting, or scaling at the labial commissure(s). Patients may complain of burning and discomfort opening the mouth wide (Table 32-1).
- III. WORKUP** Thorough history and physical examination may provide information about eating disorders, nutritional status, underlying medical conditions such as Crohn disease, acrodermatitis enteropathica, diabetes mellitus, or HIV. Inspection for dentures, mandibular alveolar vertical bone loss, and gingival or palatal erythema may suggest candidiasis and denture stomatitis. Superimposed infection with *C. albicans* or staphylococcus may play a role; culture testing of a lesion may be helpful but interpretation may be challenging due to the abundance of normal oral flora. Evaluation for nasal colonization of staphylococcus may be helpful (Table 32-2).
- IV. TREATMENT** Successful therapy requires the identification and correction of any potential underlying factors. If no underlying cause is identified, a trial of one or more of the following measures is appropriate. Ointment vehicles are preferable to creams or lotions (Table 32-3).
- A. Topical Antifungals.** The imidazoles and broader spectrum triazoles are used most often in underlying candidal infections. The polyene antibiotic nystatin is also effective. Tolnaftate (Tinactin) and undecylenic acid (Cruex; Desenex) are not effective against *Candida*. Application of the appropriate antifungal is recommended after meals and before bedtime.
 - B. A Mild Corticosteroid Ointment,** such as desonide 0.05%, applied twice daily will minimize inflammation and discomfort. It may be used concomitantly with topical antifungal agents.
 - C. Topical Antibiotics.** Topical mupirocin ointment applied two to four times daily until resolution is useful in treating staphylococcal colonization.



Figure 32-1. Angular cheilitis. Erythema and fissuring of the oral commissures. (From Neville BW, Damm DD, White DK, Waldron CA. *Color Atlas of Clinical Oral Pathology*. Philadelphia, PA: Lea & Febiger; 1991. Used with permission.)

TABLE 32-1	Differential Diagnosis
<ul style="list-style-type: none">• Actinic cheilitis• Granulomatous cheilitis• Allergic contact dermatitis• Lip-licking dermatitis• Herpes simplex virus	

TABLE 32-2	Laboratory Workup
<ul style="list-style-type: none">B12FolateIronFasting glucoseCulture	

TABLE 32-3	Primary Treatment Options
<ul style="list-style-type: none">1. Topical antifungals<ul style="list-style-type: none">a. Imidazoles—ketoconazole, miconazole, clotrimazoleb. Triazoles—fluconazole, itraconazole2. Topical antibiotics (mupirocin)3. Denture care	

- D. Denture Care.** Dentures should be removed at night and thoroughly cleansed before reinserting in the morning. Dilute bleach solution, sodium benzoate, or chlorhexidine mouth rinse are good antimicrobial options. Significant loss of vertical alveolar ridge height may need to be addressed by a dental prosthodontist to aid in restoration of soft tissue support. Petrolatum can be used as a mechanical barrier.
- E. Soft Tissue Augmentation with Dermal Fillers** to correct redundant tissue folds often alleviates mechanical factors.
- F. Nutrition.** If nutritional analysis and investigations reveal specific deficiencies, targeted supplementation is indicated.

Suggested Readings

- Fotos PG, Lilly JP. Clinical management of oral and perioral candidiasis. *Dermatol Clin.* 1996;14:273-280.
- Lu DP. Prosthodontic management of angular cheilitis and persistent drooling: a case report. *Compend Contin Educ Dent.* 2007;28:572-577.
- MacFarlane TW, Helnarska SJ. The microbiology of angular cheilitis. *Br Dent J.* 1976;140:403-406.
- Rogers RS III, Bekic M. Diseases of the lips. *Semin Cutan Med Surg.* 1997;16:325-326.
- Sharon V, Fazel N. Oral candidiasis and angular cheilitis. *Dermatol Ther.* 2010;23:230-242.

I. BACKGROUND Pityriasis rosea (PR) is a mild self-limited eruption seen predominantly in adolescents and young adults during the spring and fall. A viral etiology for PR has often been suggested, although there has been inconsistent supporting laboratory evidence. A number of studies suggested a role for human herpesvirus 7 (HHV-7)¹ while others have failed to find serologic or tissue-based evidence for HHV-7 in patients with PR.² Other studies have implicated HHV-6 as a possible cause.³ Recently, HHV-6 and the influenza A (H1N1) viruses were found to have possible implications in the pathogenesis of PR.⁴ More studies are required before the etiology can be resolved.

PR may be asymptomatic, but many patients will experience pruritus, which at times can be severe. The onset of the eruption is sometimes coincident with mild malaise and symptoms similar to those of a viral upper respiratory tract infection or gastrointestinal symptoms (<20% of patients report some preceding viral symptoms).

II. CLINICAL PRESENTATION The initial lesion is frequently a 2- to 6-cm, round, erythematous, pink- to salmon-colored scaling patch or plaque, which may appear anywhere on the body but most commonly on the trunk (about 50%), more rarely on the limbs. The collarette of scale is described as “trailing,” with the free edge pointing inward (Fig. 33-1). This “herald patch” or “mother patch” is not present, or at least not noticed, in 20% to 30% of cases. The patch can enlarge progressively to reach a diameter of 3 cm or more. Within several days to 2 weeks, a more generalized eruption can develop consisting of small 1- to 2-cm pale, red, round to oval macular and papular lesions with a crinkly surface and a rim of fine scale which appear in crops on the trunk and proximal extremities (Fig. 33-2). Minute pustules may also be seen. The face, hands, and feet are usually spared, except in children. The long axes of the lesions are oriented in the planes of cleavage running parallel to the ribs and are classically said to form a Christmas tree-like pattern (Fig. 33-3). Lesions may be few or almost confluent, slowly enlarging by peripheral extension, and can continue to appear for 7 to 10 days. Oral lesions are unusual, but when present consist of red patches and plaques with hemorrhagic puncta or white erosions. Annular lesions have also been described in the mucosa.

Variants of PR at times seem to appear as commonly as the classic disease. In children, the lesions are often papular, and purpuric lesions have also been described. Vesicular and bullous lesions may be seen, often with involvement of the palms and soles. Occasionally, eruptions may be limited to a small area or confined only to skin folds, which is known as *inverse* PR. Urticarial, intensely inflammatory, and very symptomatic lesions are possible. The herald patch may be absent, not noticed, or the only manifestation of the disease. In patients



Figure 33-1. Pityriasis rosea: This patient has a herald patch on her chest. Other smaller lesions can be seen. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 33-2. Pityriasis rosea: Multiple lesions with fine scale. Note the elliptic ("football") shape of lesions. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 33-3. Pityriasis rosea causes a papulosquamous eruption that frequently involves the thorax and assumes a characteristic “Christmas tree” appearance. (From Fleisher GR, Ludwig S, Baskin MN. *Atlas of Pediatric Emergency Medicine*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

with Fitzpatrick skin types IV and V, individual lesions may have more of a lichenoid appearance and may show more depigmentation. The distribution may be atypical, often including the face. Either hyper- or hypopigmentation may persist after the initial eruption has resolved.

III. WORKUP The diagnosis of PR is usually made with clinical observation (Table 33-1). Except in its atypical forms, the eruption is usually easily diagnosed by its morphology and distribution. Dermoscopy can be particularly helpful in the evaluation of unusual presentations by improving visualization of vessels and color which may be difficult to observe with the naked eye. A serologic test for syphilis should be considered for all patients, because secondary syphilis may closely mimic PR. Other differential diagnostic considerations include guttate and acute psoriasis, nummular eczema, tinea corporis, seborrheic dermatitis, tinea versicolor, Gianotti-Crosti syndrome, pityriasis lichenoides, erythema annulare centrifugum, and scabies infestation.

Medications have been implicated in causing PR-like eruptions: (i) captopril or other angiotensin-converting enzyme (ACE) inhibitors, (ii) arsenicals, (iii) bismuth, (iv) tripeleminamine HCl, (v) methoxypromazine, (vi) barbiturates, (vii) clonidine, (viii) nonsteroidal anti-inflammatory drugs, (ix) metronidazole,

TABLE 33-1 **Differential Diagnosis**

- Drug eruption
- Erythema migrans (with secondary lesions)
- Erythema multiforme
- Guttate psoriasis (no marginal collarette)
- Lichen planus
- Nummular eczema
- Psoriasis
- Seborrheic dermatitis
- Secondary syphilis
- Small plaque parapsoriasis
- Tinea corporis
- Tinea versicolor
- Viral exanthem

(x) gold, (xi) bacille Calmette-Guerin (BCG) vaccination, (xii) isotretinoin, (xiii) labetalol or other β -blockers, and (xiv) D-penicillamine.

PR-like eruptions have been reported with Hodgkin disease, cutaneous T-cell lymphoma, and solid tumors (gastric and pulmonary carcinoma, most commonly). Lesions that do not resolve in 8 to 12 weeks may have pityriasis lichenoides spectrum disease (PLEVA/PLC), and a punch biopsy should be performed.

IV. TREATMENT Most patients require no treatment other than proper patient education and reassurance because the disease is usually mild and self-limited. Nevertheless, a number of therapies exist which may provide clinical benefits to patients who require therapy (Table 33-2).

A. Topical Corticosteroids or Oral Antihistamines. Patients with pruritus may benefit from topical antipruritic lotions containing menthol or pramoxine, or even low- to medium-potency topical corticosteroids (triamcinolone 0.1%) applied to the pruritic areas two or three times

TABLE 33-2 **Primary Treatment Options**

1. Topical corticosteroids or oral antihistamines
2. Ultraviolet B (UVB) phototherapy
3. Oral erythromycin
4. Acyclovir
5. Systemic corticosteroids

daily. Pruritis may also be alleviated with emollients or oral nighttime antihistamines.

- B. Ultraviolet B (UVB) Phototherapy.** For more severe disease, one to several consecutive daily doses of erythema-producing UVB light will decrease both the pruritus and the extent of the eruption in 50% of those treated. Sunlight, too, appears to have a direct beneficial effect. It has been suggested that those treated within the first week of rash will respond more readily.
- C. Oral Erythromycin.** A double-blind placebo-controlled study of 90 patients demonstrated that oral erythromycin in a dose of 250 mg four times daily in adults and 25 to 40 mg/kg in four divided doses in children (for 2 weeks) was effective in improving PR in 74% of treated patients and not in the placebo group.⁵
- D. Acyclovir.** Given the possible association between PR and HHV-6 and HHV-7, acyclovir may be considered. In a randomized trial without placebo control arm, 64 patients with PR demonstrated a dose of acyclovir 400 mg five times daily for 1 week accelerated reduction in erythema with 79% in the acyclovir group and 27% in the no treatment group.⁶ A trial using high-dose acyclovir (800 mg five times daily) cleared lesions in the treatment group in 19 days, compared with 38 days in the control group.⁷ As acyclovir is a relatively low-cost treatment and generally well tolerated, it should be considered in PR patients who exhibit flu-like symptoms with or without extensive skin disease.
- E. Systemic Corticosteroids.** Rarely, a brief course of systemic corticosteroids may be required. However, caution must be used to taper the steroids slowly to avoid rebound.

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REFERENCES

1. Rebera A, Drago F, Broccolo F. Pityriasis rosea and herpesviruses: facts and controversies. *Clin Dermatol.* 2010;28:497-501.
2. Chuh AA, Chan HH, Zawar V. Is human herpesvirus 7 the causative agent of pityriasis rosea? A critical review. *Int J Dermatol.* 2002;41:563-567.
3. Broccolo F, Drago F, Careddu AM, et al. Additional evidence that pityriasis rosea is associated with reactivation of human herpesvirus-6 and -7. *J Invest Dermatol.* 2005;124:1234-1240.
4. Mubki T, Bin Dayel S, Kadry R. A case of pityriasis rosea concurrent with the novel influenza A (H1N1) infection. *Pediatr Dermatol.* 2011;28:341-342.
5. Lallas A, Kyrgidis A, Tzellos TG, et al. Accuracy of dermoscopic criteria for the diagnosis of psoriasis, dermatitis, lichen planus, and pityriasis rosea. *Br J Dermatol.* 2012;166:1198-1205.
6. Rassai S, Feily A, Sina N, Abtahian S. Low dose of acyclovir may be an effective treatment against pityriasis rosea: a random investigator-blind clinical trial on 64 patients. *J Eur Acad Dermatol Venereol.* 2011;25:24.
7. Drago F, Vecchio F, Rebera A. Use of high-dose acyclovir in pityriasis rosea. *J Am Acad Dermatol.* 2006;54:82.

I. BACKGROUND Postinflammatory hyperpigmentation (PIH) is common in more darkly pigmented persons. It also tends to be a greater cosmetic concern in darkly pigmented individuals than it is in those with lighter skin tones. PIH can occur in any age group or gender. By definition, this form of hyperpigmentation occurs in an area that has sustained prior physical trauma. This trauma may be in the form of a dermatosis such as acne vulgaris or eczema, or it may be mechanical or chemical in nature as might occur following a traumatic cut or chemical burn. Because in most cases PIH resides at a dermal level, injuries that lead to greater disturbance of the dermal–epidermal junction can be expected to yield more profound and persistent PIH. PIH may persist for months to years, and may even be permanent in some cases.

II. CLINICAL PRESENTATION PIH may appear as macules or patches, and depending upon the nature of the insult may be well localized or extensive (Figs. 34-1 and 34-2). Linear PIH may result from trauma that occurred in a linear fashion. PIH mimicking the distribution of dermatoses has also been reported. For example, segmental PIH may occur following a herpes zoster outbreak and linear PIH may result from a dermatosis that follows Blaschko lines. PIH is asymptomatic.



Figure 34-1. Acne. Postinflammatory hyperpigmentation is seen in this African American patient. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 34-2. Postinflammatory hyperpigmentation. This patient has atopic dermatitis that has resolved with hyperpigmentation. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

III. WORKUP PIH does not require any extensive workup. The clinical findings are usually supported by the history of antecedent trauma described by the patient. At times, it is useful to examine pigmentary lesions under Wood light. When pigment is present in the epidermis, the contrast between normal and hyperpigmented skin is enhanced. When pigment is present in the dermis, the contrast is not enhanced compared with ambient visible light.

IV. TREATMENT (Table 34-1)

A. Sun Protection. Given the ability of ultraviolet light to darken lesions of PIH, strict avoidance of sunlight on the affected area is imperative. If strict sun avoidance is not an alternative, then at minimum the patient should apply a broad-spectrum sunscreen with an SPF of 15 or greater to the affected area on a daily basis. The patient should be careful to reapply the sunscreen every 2 to 3 hours, especially if they are outdoors and exposed to sunlight. Sun protection is an important “first step” to take for this problem regardless of any other treatment options that might be used to lighten the excess pigment.

B. Topical Bleaching Agents

- 1. Hydroquinone (HQ) Alone.** The intensity of pigmentation in PIH may be decreased by the regular application of 2% to 5% HQ cream or lotion b.i.d. for weeks to months. HQ over the counter is usually 2%; 4% is the

typical concentration prescribed by dermatologists, although pharmacists can mix concentrations up to 10%. HQ is thought to act by (i) competing with tyrosine oxidation by acting as an alternate substrate for tyrosinase, the enzyme that converts tyrosine to melanin, and (ii) selective damage to melanosomes and melanocytes. Four to 6 weeks of monotherapy are required before depigmenting effects are seen. The hyperpigmented areas fade more rapidly and completely than the surrounding normal skin. The most common side effects are skin irritation and contact dermatitis. A rare side effect is the development of exogenous ochronosis which can be extremely difficult to reverse. It is thought to result from the extended use of HQ, with the greatest risk in dark-complected individuals living in sunny climates. Alternating HQ in 4-month cycles with other depigmenting agents can prevent or reduce side effects.

2. Azelaic acid is a naturally occurring dicarboxylic acid derived from *Pityrosporum ovale*. It is available in strengths of 15% to 20% in the United States by prescription. It is applied b.i.d. for 3 to 12 months and is generally well tolerated.
3. Kojic acid, arbutin, licorice extract, and soy extracts have all been touted as alternatives to HQ for treating hyperpigmentation. They are found in many over-the-counter cosmeceutical preparations and work to varying degrees. None of them appear to equal HQ in efficacy and speed of improving PIH.

C. Chemical Peels. The use of superficial to medium depth chemical peels has also been found to be useful in treating PIH. Salicylic and glycolic acid peels, repeated every 4 to 6 weeks, have been found to stimulate melanosome turnover and improve hyperpigmentation. Jessner solution can decrease PIH. Medium depth chemical peels with 25% to 35% trichloroacetic acid have also been used effectively, although they carry a higher risk of worsening hyperpigmentation or causing hypopigmentation. Chemical peels have also been found to exfoliate the epidermis enough to allow better penetration of topical bleaching creams such as HQ, thus boosting their efficacy. Pretreatment with HQ has also been reported to decrease the risk of hyperpigmentation following a chemical peel.

D. Laser/Light Therapy. Treatment with the Q-switched ruby, Q-switched alexandrite, and Q-switched Nd:YAG lasers have been found to be effective in some patients with pigmentary disorders such as PIH. Q-Switched Nd: YAG lasers at lower fluence settings have been shown to be more effective compared to higher fluence settings. Nonablative fractional resurfacing lasers may also be used to treat different forms

TABLE 34-1 Primary Treatment Options for PIH

Sunscreen—broad spectrum, SPF 15+
Topical hydroquinone
Chemical peels
Lasers

of hyperpigmentation. These lasers all target melanocytes or water and decrease hyperpigmentation, theoretically leaving the skin intact without scarring. However, the use of any laser can carry a risk of postinflammatory hypo- or hyperpigmentation, scarring, and even keloid formation.

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Suggested Readings

- Alajlan AM, Alsuwaidan SN. Acne scars in ethnic skin treated with both non-ablative fractional 1,550 nm and ablative fractional CO₂ lasers: comparative retrospective analysis with recommended guidelines. *Lasers Surg Med.* 2011;43(8):787-791.
- Hexsel D, Arellano I, Rendon M. Ethnic considerations in the treatment of Hispanic and Latin-American patients with hyperpigmentation. *Br J Dermatol.* 2006;156(Suppl 1):7-12.
- Toombs EL, guest ed. Treatment of problems unique to ethnic skin and hair. *Dermatol Therapy.* 2007;20(3):121-156.
- Woolery-Lloyd H, Kammer JN. Treatment of hyperpigmentation. *Semin Cutaneous Med Surg.* 2011;30(3):171-175.

I. BACKGROUND Pruritus, or itch, is a sensation that leads to scratching. It can be acute or chronic (lasting more than 6 weeks), localized or generalized, and is broadly categorized neuroanatomically as pruritoceptive, neuropathic, neurogenic, or psychogenic. Itch is the most common symptom in many inflammatory skin diseases (e.g., atopic dermatitis, contact dermatitis, and psoriasis) and infectious skin diseases (e.g., chickenpox), but it may also be associated with systemic diseases (e.g., chronic renal failure, HIV, cutaneous T-cell lymphoma) or simply xerosis. Because it is a subjective experience that is associated with a variety of conditions, it is difficult to estimate the incidence and prevalence of pruritus.

II. CLINICAL PRESENTATION Pruritus provokes patients to scratch or rub their skin, which serves to potentiate the vicious scratch–itch cycle. Consequently, areas of itching may eventually manifest as areas of bleeding, excoriations, ulcerations, and crusts. Further scratching results in lichenification with changes in skin pigmentation as well as scar formation. Chronic pruritus may lead to hyperpigmented plaques and excoriated nodules resembling prurigo nodularis (Figs. 35-1 to 35-3) (Table 35-1).

III. WORKUP Pruritus is a subjective perception described by the patient. In order to properly treat pruritus, the underlying cause must be elicited through a thorough history, physical examination, and a diagnostic workup. History should include location, onset, timing, duration, and character of the itch, as well as alleviating/aggravating factors and patient characteristics (e.g., age, medications, allergies, and signs of systemic disease). In addition to careful examination of the skin, nails, scalp, hair, and mucous membranes, a physical examination should also include palpation of lymph nodes, thyroid gland, and abdomen. Initial laboratory investigations should include a complete blood count with differential, as well as liver, renal, and thyroid function tests and urinalysis. Additional tests, such as anemia analysis, HIV, chest x-ray, and abdominal ultrasound, may also be necessary (Table 35-2).

IV. TREATMENT Treatment of pruritus is aimed at relieving symptoms, eliminating the cause, and breaking the itch–scratch cycle. Generally, topical medications are used for mild, localized itch; systemic therapies may be necessary for severe, generalized itch. Many patients require a combination (Table 35-3). Regardless of treatment option, it is important to offer patients practical advice consistent with eczema skin care, such as limiting shower time, bathing in lukewarm water, keeping fingernails short, and using mild cleansers.



Figure 35-1. Notalgia paresthetica. The postinflammatory hyperpigmentation resulted from the chronic rubbing and scratching of this itchy area. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 35-2. HIV-associated eosinophilic folliculitis. Intensely pruritic excoriated and nonexcoriated papules are present on this patient's upper back. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

A. Topical Treatments. Topical therapy is important in the management of acute pruritus as well as more generalized pruritus in patients who may not be candidates for systemic therapy.

- 1. Moisturizers.** Moisturizers alleviate itching by improving the barrier function of the skin, specifically by controlling transepidermal water



Figure 35-3. Prurigo nodularis. These intensely pruritic excoriated papules on the pretibial shafts show marked postinflammatory hyperpigmentation. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

TABLE 35-1 **Examples of Pruritus**

1. Dermatologic

- a. Inflammatory (contact dermatitis, nummular eczema, psoriasis, drug reactions, mastocytosis)
- b. Infections (scabies, tinea corporis, impetigo)
- c. Cutaneous T-cell lymphomas

2. Systemic

- a. Endocrine and metabolic disorders (renal, liver, and thyroid diseases)
- b. Infections (HIV, parasites, HCV)
- c. Hematologic (polycythemia vera)
- d. Solid organ tumors

3. Neurologic (multiple sclerosis, notalgia paresthetica, brachioradial pruritus)

4. Psychogenic

TABLE 35-2	Laboratory Workup
Complete blood count with differential	
Liver, kidney, and thyroid function tests	
Analysis of anemia	
Chest x-ray	
Abdominal ultrasound	

TABLE 35-3	Primary Treatment Options
1. Topical	
a. Moisturizers	
b. Corticosteroids (flucinomide)	
c. Calcineurin inhibitors (tacrolimus, pimecrolimus)	
d. Antihistamines (doxepin)	
e. Neuromodulators (pramoxine, lidocaine, capsaicin, menthol)	
2. Systemic	
a. Antihistamines (fexofenadine, loratadine, cetirizine)	
b. Glucocorticosteroids	
c. Antidepressants (SSRIs)	
d. Anticonvulsants (gabapentin)	
e. Phototherapies (UVA, UVB, PUVA)	

loss. They are of proven benefit in xerosis, atopic dermatitis, allergic contact dermatitis, and psoriasis and may be beneficial to all patients suffering from pruritus. Patients should be advised to apply moisturizers one to three times daily and especially after bathing. Generally, thick creams with high lipid content are preferred to thinner lotions.

- 2. Corticosteroids.** Topical corticosteroids are powerful first-line drugs effective in moderate-to-severe inflammatory skin diseases, but they may provide no relief to patients with noninflammatory pruritus. Topical corticosteroids are only recommended for short-term use of 1 to 3 weeks. Lower potency corticosteroids may be applied to the face or intertriginous areas, while higher potency agents should be restricted to the trunk or extremities. Used correctly, topical corticosteroids will provide fast relief. In one study, fluocinonide 0.1% cream (a class I ultra-high-potency corticosteroid) applied two times a day for 3 days yielded a 79% decrease in pruritus.¹ Because of their potency, topical steroids are

not for generalized, chronic use. Side effects include atrophy, telangiectasia, and risks associated with systemic absorption.

3. **Calcineurin Inhibitors.** Tacrolimus 0.03% and 0.1% ointment and pimecrolimus 1% cream are often effective at relieving pruritus in atopic dermatitis and anogenital pruritus. Although topical calcineurin inhibitors may induce short-lived burning or stinging sensations, they may be safely used on the face, genitals, and intertriginous areas, unlike topical corticosteroids. Studies have not shown an increase in immunosuppression or grave infections with chronic use.
 4. **Antihistamines.** Doxepin, a tricyclic antidepressant, is the only topical antihistamine that has been shown to be effective in relieving pruritus in patients with atopic dermatitis, lichen simplex chronicus, contact dermatitis, and nummular dermatitis. Unfortunately, it is limited by side effects of localized cutaneous burning, allergic contact dermatitis, and drowsiness.
 5. **Neuromodulators.** Pramoxine 1%, lidocaine 5%, and eutectic lidocaine 2.5%–prilocaine 2.5% are local anesthetics that may relieve pruritus associated with neuralgia paresthetica (Fig. 35-1), pruritus ani, and postburn pruritus. In an open-label study, a combination of 5% urea and 3% polidocanol, which has both local anesthetic properties and moisturizing effects, significantly reduced or eliminated pruritus in patients with atopic dermatitis, psoriasis, and contact dermatitis.² Topical capsaicin, which acts through TRPV1 to release substance P, has been successful in relieving chronic, localized pruritus, such as that associated with prurigo nodularis, neuralgia paresthetica, and aquagenic pruritus. Initially, the drug may effect a localized but very intense burning sensation, but this resolves after a few days. Patients should be warned, as this side effect may induce poor compliance. Topical menthol, a drug with both antipruritic and analgesic properties, may be effective for some patients. Available over-the-counter, cooling agents such as menthol 1% to 3% (e.g., Sarna Lotion) provide short-term relief. Greater doses of menthol, however, have been associated with increased irritation.
- B. Systemic Treatments.** Various therapies are available, but no one drug has been proven to be the best in terms of both efficacy and safety.
1. **Antihistamines.** Nonsedative or mildly sedative H1R antagonists (e.g., fexofenadine 180 mg; loratadine 10 mg; cetirizine 10 mg) are used to treat pruritus in urticaria during the day while sedating antihistamines (e.g., hydroxyzine) are typically used at night. However, efficacy may decrease with increased levels of histamine release, and consequently, other modes of treatment will need to be pursued. Topical doxepin 5% has been shown to be effective in the treatment of chronic pruritus and may be used as an alternative, but it may cause allergic contact dermatitis.³
 2. **Glucocorticosteroids.** Systemic glucocorticosteroids (SGCs) starting at 0.5 to 2.0 mg/kg have been effective in treating pruritus in diseases such as bullous pemphigoid, psoriasis, and urticaria, but their usage is limited by multiple adverse side effects (e.g., adrenal suppression, hyperglycemia, infections, mental dysfunction). Patients should be started simultaneously on an appropriate alternative therapy and the dosage of the SGC should be tapered. Other immunosuppressants, such as

cyclosporine A (starting at 3 to 5 mg/kg and reduced to 3 mg/kg), may be a better choice than SGCs for long-term use.

3. **Antidepressants.** Selective serotonin-reuptake inhibitors paroxetine, fluvoxamine, and sertraline have been used to treat pruritus in patients with diseases such as atopic dermatitis, prurigo, and polycythemia vera. Oral doxepin (starting at 10 mg and increased every 3 days until sedation is intolerable) is effective in patients with renal itch, atopic dermatitis, noninflammatory dermatoses, and HIV-induced pruritus and is considered a second- or third-line therapy.
4. **Anticonvulsants.** Gabapentin (900 to 3,600 mg daily) has been shown to be effective in treating prurigo, senile pruritus, brachioradial pruritus, cutaneous T-cell lymphoma, notalgia paresthetica, as well as liver-associated and renal itch. However, gabapentin should be avoided in patients with cholestasis, as it has been shown to be associated with increased pruritus.⁴
5. **Phototherapies.** UV therapy (UVA, UVB, psoralen UV) is effective in treating chronic pruritus of inflammatory dermatoses, cutaneous T-cell lymphoma, renal itch, and liver-associated itch. Phototherapy should particularly be considered for use during pregnancy as an alternative for pruritus that is resistant to histamine or steroid treatment.

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REFERENCES

1. Yentzer BA, Ade RA, Fountain JM, et al. Improvement in treatment adherence with a 3-day course of fluocinonide cream 0.1% for atopic dermatitis. *Cutis*. 2010;86:208-213.
2. Freitag G, Hoppner T. Results of a postmarketing drug monitoring survey with a polidocanol-urea preparation for dry, itching skin. *Curr Med Res Opin*. 1997;13:529-537.
3. Eschler DC, Klein PA. An evidence-based review of the efficacy of topical antihistamines in the relief of pruritus. *J Drugs Dermatol*. 2010;9:992-997.
4. Bergasa NV, McGee M, Ginsburg IH, Engler D. Gabapentin in patients with the pruritus of cholestasis: a double-blind, randomized, placebo-controlled trial. *Hepatology*. 2006;44:1317-1323.

Suggested Readings

- Cassano N, Tessari G, Vena G, Girololmoni G. Chronic pruritus in the absence of specific skin disease. *Am J Clin Dermatol*. 2010;11:399-411.
- Shnaker BF, McAuely JW. Pregabalin: a new neuromodulator with broad therapeutic indications. *Ann Pharmacoter*. 2005;141:1507-1509.

I. BACKGROUND Psoriasis is a chronic proliferative epidermal disease with no cure. The cause is unknown. It affects up to 8 million people in the United States and 1% to 3% of the world's population. Psoriasis typically begins in the third decade of life but can develop anytime from birth onward. A family history of psoriasis is found in 30% of affected patients. A multifactorial mode of inheritance is most likely. The histocompatibility antigen HLA-Cw6 is most strongly associated with psoriasis (relative risk is 24).

Psoriasis is due to a chronic T-cell-mediated inflammation within the psoriatic plaque. Antigen-presenting cells (APCs) in the skin are activated by unknown antigens and travel to the lymph nodes. In the lymph nodes, APCs in turn activate T cells and program these T cells to home back to the skin. Once in the skin, these activated T cells, APCs, and keratinocytes produce inflammatory cytokines including IL-12, 17, and 23, tumor necrosis factor- α , and IFN- γ causing epidermal hyperproliferation and the formation of the psoriatic plaque.

Hyperstimulated psoriatic keratinocytes travel from the basal cell layer to the surface in 3 to 4 days, much more rapidly than the normal 28 days. Decreased keratinocyte transit time does not allow for normal maturation and keratinization. This is reflected clinically by scaling, a thickened epidermis with increased mitotic activity, and by the presence of the immature nucleated cells in the stratum corneum.

II. CLINICAL PRESENTATION Psoriasis is chronic and usually remains as discrete localized plaques in the majority of patients. Extensive or generalized involvement may occur in up to 25% of patients. Spontaneous clearing is rare, but unexplained exacerbation or improvement is common. Stress, viral (including HIV), or bacterial illness may precede flare-ups. Alcohol and smoking can also exacerbate the disease.

Most lesions of psoriasis are asymptomatic, but pruritus may be noted in up to 20% of patients. Those with generalized disease may resemble an exfoliative dermatitis with loss of thermoregulation leading to a feeling of chills and shivering, increased protein catabolism, and cardiac stress.

Up to 30% of patients may develop psoriatic arthritis (PsA). This is most commonly manifested by oligoarticular or polyarticular asymmetric joint pain in the small joints of the hands, feet, and spine. However, larger joints may be affected.

The classic psoriatic lesion is an erythematous, sharply circumscribed plaque covered by loosely adherent, silvery scales (Figs. 36-1 and 36-2). Acute lesions tend to be small and guttate (dewdrop shaped) (Fig. 36-3). Pinpoint bleeding can be seen when the scale is removed (Auspitz sign). Any body area may be involved, but lesions tend to occur most often on the elbow, knees,



Figure 36-1. Thick “psoriasiform” lesions are on the extensor forearms in this patient. (From Goodheart HP. *Goodheart’s Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 36-2. These lesions with whitish, micaceous scale are seen in a typical location. (From Goodheart HP. *Goodheart’s Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 36-3. Psoriasis (acute guttate). This 11-year-old child had recent group A beta-hemolytic streptococcal pharyngitis. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

scalp, genitalia, and intergluteal cleft. The lesions may also occur in areas of epidermal injury (the Koebner reaction) such as in scratches, scars, or sunburns.

Nail involvement (pitting, yellow-brown discoloration, subungual hyperkeratosis) can be seen in up to 50% of patients with psoriasis and in most patients with PsA of the hands and feet (Fig. 36-4).



Figure 36-4. Psoriasis “oil spots” or “drops.” Orange-brown coloration appears under the nail plate, presumably the result of psoriasis of the nail bed. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 36-5. Psoriasis. Erythrodermic variant. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

Exfoliative (erythrodermic) psoriasis resembles other exfoliative dermatoses. It may occur spontaneously, follow a systemic illness or drug reaction, or occur as a reaction to steroid withdrawal (Fig. 36-5).

Pustular psoriasis occurs in several forms: acute (von Zumbusch), subacute annular, and chronic acral (Fig. 36-6). The pustules are sterile. Flare-ups may be precipitated by infection or recent use of systemic corticosteroids. Impetigo herpetiformis is a rare form of pustular psoriasis during pregnancy.

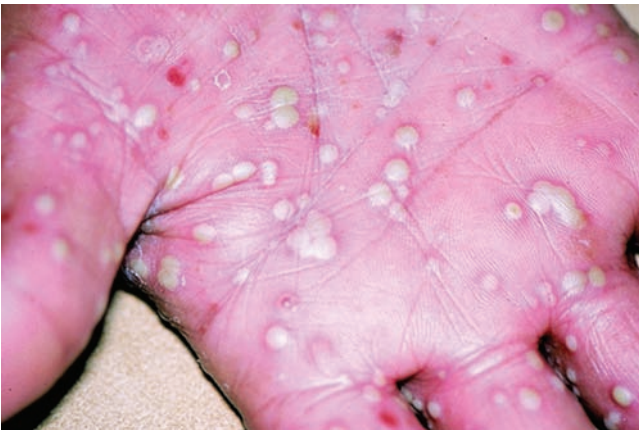


Figure 36-6. Psoriasis. This is the pustular variant of psoriasis. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

PsA is characterized by inflammation in and around the joints of the wrists, fingers, knees, ankles, lower back, and neck. It is equally common in both men and women with the age of onset typically between 30 and 55 years old. The rheumatoid factor is usually negative; 25% to 30% of psoriasis patients will develop PsA. It may appear up to 10 years after the first signs of skin involvement and in 85% of patients with PsA the skin disease precedes the arthritis.

PsA classically involves the distal interphalangeal joint and may be acute causing erythema and swelling of the distal phalanx causing a “sausage” appearance (dactylitis) (Fig. 36-7).

Fifty percent of patients have asymmetric oligoarticular disease (affecting less than or equal to four joints), 25% have symmetric disease, 25% have spondyloarthritis with or without peripheral arthritis, and 5% have a destructive polyarthritis (arthritis mutilans) (Fig. 36-8).

Chronic arthritis leads to progressive permanent bone and joint destruction (Fig. 36-9).^{1,2}

The CASPAR classification criteria are a very specific (98.7%) and sensitive (91.4%) way to diagnose PsA.³ Using the CASPAR system, a patient with **inflammatory articular disease** of the joints, spine, or tendons (enthesitis) **plus** a score of **3** or more points from the following supports the diagnosis of PsA (Table 36-1).



Figure 36-7. Psoriatic arthritis. “Sausage finger deformity” of the distal interphalangeal joint. Note onycholysis. (From Goodheart HP. *Goodheart’s Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 36-8. Psoriatic arthritis (“arthritis mutilans”). This patient has severe psoriatic arthritis with marked deformities and subluxations of the small bones of the hands. Note also the characteristic onycholysis on the nails. (From Goodheart HP. *Goodheart’s Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

III. WORKUP The diagnosis of psoriasis is mainly a clinical one. Preceding streptococcal pharyngitis is often the cause of acute guttate disease. Family history of psoriasis can be helpful.

Medications such as lithium, antimalarials, β -blockers, NSAIDs, and the statins have been implicated to cause flares. When in doubt, a skin biopsy may be helpful.

Patients with PsA typically have an elevated erythrocyte sedimentation rate and a negative test for rheumatoid factor. X-ray films of the hands may show subcortical cystic changes with relative sparing of the articular cartilage.

Many patients have associated metabolic syndrome with obesity, hypertension, and hyperlipidemia.

IV. TREATMENT

A. General Principles. When deciding on what therapy to begin with, it is important to involve the patient in the decision-making process. The treatment is usually chronic so the patient must be comfortable and compliant with the therapy to achieve success. Many psoriasis patients have other underlying medical problems including obesity, hypertension, and hyperlipidemia. These problems must be assessed in order to determine whether systemic treatment is appropriate. The extent of disease involvement may be limited, but if it is impairing the quality of life, a more aggressive systemic therapy may be warranted.

B. Basic Approach to Managing a Patient with Psoriasis. Below are some treatment suggestions for different types of patients. The clinician must use his/her clinical judgment as to the best approach to ultimately use.

1. Localized Disease (<5% BSA)

a. Topical Therapy:



Figure 36-9. Psoriatic arthritis: ray pattern. PsA hand. Note the erosive changes are present at the three joints of the second digit (arrows). This pattern of arthritis is virtually diagnostic of psoriasis. Also note the involvement of the first ray. (Yochum TR, Rowe LJ. *Yochum and Rowe's Essentials of Skeletal Radiology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

TABLE 36-1 CASPAR Criteria for Psoriatic Arthritis

	Points
1. Evidence of psoriasis (one of the following)	
Current psoriasis	2
Personal history of psoriasis	1
Family history of psoriasis	1
2. Psoriatic nail dystrophy (may include the following)	
Onycholysis, pitting, or hyperkeratosis	1
3. Negative test for the rheumatoid factor	1
4. Dactylitis (one of the following)	1
Current dactylitis	
History of dactylitis	
5. Radiologic evidence of juxta-articular new bone formation	1

- These can be used alone for localized disease or in combination with systemic medications or phototherapy for more extensive disease.
- Excellent for pregnant women and children.
 - i. Potent topical steroids applied bid to localized lesions are helpful. Overnight occlusive therapy with these medications using plastic wrap or gloves for 2 weeks will initiate involution in most lesions. Topical steroids inhibit mitosis and lymphokines reducing inflammation and epidermal proliferation.
 - Apply topical steroids without occlusion during the day.
 - As lesions subside, decrease the use of occlusion and increase the use of bland emollients (Eucerin, Aquaphor, petrolatum). After lesions have flattened, apply corticosteroids in bursts (several days on than several days off).
 - Avoid using potent topical steroids in body folds or the face.
 - If superpotent topical steroids are used, they should be applied to limited areas only, and after achieving the desired results, they should be switched to an intermittent or staggered regimen. Suppression of the hypothalamic pituitary axis can occur with as little as 2 g per day of topical super potent steroids such as clobetasol proportionate.
 - ii. Topical vitamin D analogs (calcipotriene, calcitriol) are especially helpful for the genitals and intertriginous areas but can be irritating when used on the face.
 - Mode of action is inhibition of epidermal proliferation and induction of normal epidermal differentiation by enhancing cornified envelope formation and activating transglutaminase.
 - Avoid using more than 100 g per week to minimize the risk of kidney stones.
 - A safe and effective regimen is calcipotriene ointment bid Monday through Friday, adding clobetasol ointment with the calcipotriene bid Saturday and Sunday. To prevent skin atrophy, avoid using clobetasol in the body folds.
 - Combining calcipotriene ointment with Narrow-Band Ultra-Violet-B (NBUB) phototherapy is more effective than phototherapy alone.
 - Calcipotriene/betamethasone dipropionate combination ointment for the body and solution for the scalp is a very useful alternative for localized disease. This combination product can be used nightly for up to 1 year with minimal risk of atrophy or adrenal gland suppression. It should be avoided in intertriginous areas such as the groin and axillas and not used on the face.
 - iii. Topical tazarotene gel and cream (0.05% and 0.1%).
 - Are topical retinoids that modulate abnormal epidermal differentiation and proliferation.
 - Systemic absorption is minimal but is category X in pregnancy so use with caution in women of childbearing potential.
 - Because it can be irritating, use nightly in combination with a topical steroid such as fluocinonide or mometasone.
 - Best for localized thick plaques on trunk and extremities.

- iv. Coal tar therapy.
 - Tar inhibits DNA synthesis and has an atrophogenic effect on the skin.
 - Liquor carbonis detergens (LCD) is a refined tar that can be compounded with topical steroids and antikeratolytics; 10% LCD plus 5% lactic acid in fluocinonide ointment 0.05% applied once to twice daily is an effective compound for plaque disease.
 - Using the LCD compound at night followed by NBUVB in the morning can be very effective for plaque disease.
 - The main drawback is that it can be messy and stain clothing.
 - v. Topical tacrolimus or pimecrolimus.
 - Can be effective when used in body folds and on the face but not very effective for typical plaque psoriasis
 - Applied twice daily to the affected area
2. **Pregnant Women**
 - Consider using mild to mid-potent topical steroids first. If the disease is widespread, then consider NBUVB Phototherapy. Consultation with the obstetrician before initiating phototherapy would be recommended.
 3. **Diffuse Disease (>5% BSA)**
 - Phototherapy—see below
 - Systemic medications—see below
 4. **Scalp Psoriasis**
 - Topical fluocinolone acetone oil (Derma-Smoother) nightly for 2 to 3 weeks then twice a week as maintenance—works best if applied to a damp scalp and occluded with a shower cap
 - Topical calcipotriene/betamethasone dipropionate oil nightly and washed off in the morning
 - Calcipotriene solution 0.005% nightly Monday through Friday and clobetasol solution or foam nightly Saturday and Sunday
 - For stubborn diffuse scalp disease, consider methotrexate or the biologics
 5. **Nail Psoriasis**
 - Nail psoriasis does not respond well to topical steroids. If the involvement is significant, systemic medications with either methotrexate or the biologics should be considered.
 6. **Erythrodermic/Exfoliative Psoriasis**
 - As these patients are often febrile and very uncomfortable, a short course of cyclosporine for 3 to 4 months is very effective to “rescue” them. After the skin is controlled, can be used to one of the biologics for long-term control.
 7. **Guttate Psoriasis**
 - This form of psoriasis responds best to NBUVB phototherapy or systemic medication (MTX, biologics, cyclosporine).
 8. **Pustular Psoriasis**
 - Typically involves the palms and soles but rarely can be disseminated
 - Treatment options include oral acitretin, cyclosporine, and the biologics
 9. **Palmer/Plantar Psoriasis**
 - Responds very well to oral acitretin with or without NBUVB phototherapy.

- Biologic medications.
- If systemic medications are not an option, potent topical steroids at night under vinyl gloves for 2 to 3 weeks followed by two nights per week maintenance can be tried.

UVB phototherapy

- Typically used for more severe or widespread involvement.
- Involves the repeated exposure to ultraviolet light in the broad UVB wavelength range (290 to 320 nm) or NBUVB range (311 to 313 nm).
- A standardized three times weekly protocol will induce complete or near complete clearing in an average of 23 treatments.
- UVB phototherapy inhibits epidermal mitosis resulting in clearing of the psoriasis plaques.
- NBUVB is the newest form of phototherapy.
 - Utilizes a narrow-band wavelength of 311 to 313 nm, the wavelength determined to be the most effective in psoriasis.
 - Because it has only been in use for two decades, its long-term side effects are not yet known.
 - Is clinically more effective and felt to be less carcinogenic than either broadband UVB or PUVA (oral psoralen plus UVA).
 - In a large recent British study, no significant association between NBUVB treatment and basal cell carcinoma, squamous cell carcinoma, or melanoma was found.⁴
- 308 nm excimer laser
 - Targeted treatment using 1 to 2 cm handpiece
 - Used for treatment resistant localized plaques
 - Not practical for widespread disease
 - Can use higher doses of UV energy than conventional NBUVB resulting in fewer treatments and less overall cumulative doses theoretically reducing the risk of carcinogenesis

C. Photochemotherapy (PUVA)

- Is a combination of broadband UVA light (320 to 400 nm) with oral psoralen.
- Psoralen is a photoactive drug which forms photoadducts with DNA in the presence of UVA. This reduces the increased epidermal turnover seen in psoriasis.
- Repeated PUVA treatments clear most widespread psoriasis in 10 to 20 treatments over 4 to 8 weeks.
- As in all forms of phototherapy, maintenance treatments of once weekly to every other week are needed to maintain clearing.
- Long-term side effects include increased risk of squamous cell carcinoma, malignant melanoma, atypical pigmentation, and accelerated skin aging.
- As a result of the carcinogenic risks, PUVA has largely been replaced by NBUVB phototherapy in most patients.

D. Oral Systemic Agents^{5,6} (Table 36-2)

1. Acitretin

- Is a synthetic derivative of vitamin A.
- The usual starting dose is 10 to 20 mg per day with a maximum of 50 mg daily.

TABLE 36-2 How to Choose between Systemic Agents

Patient Situation	Therapy to Consider
Need to quickly “rescue” patient	Cyclosporine A
Prescription payment issues	MTX; UV
Obesity	Biologics; retinoids; UV
Psoriatic arthritis	Anti-TNF biologic; MTX
Neurologic abnormalities	MTX; retinoids; UV; Ustekinumab
Grade 3–4 CHF	Retinoids; MTX; UV
Hepatitis C	Anti-TNFs (consult with hepatologist); UV
History of malignancy	MTX; retinoids; UV
Frequent infections	Retinoids; UV
Dyslipidemias	UV; biologics; MTX
Pregnancy	Topical steroids; UV—always best to consult with obstetrician

- Is especially helpful as a monotherapy for palmer/plantar psoriasis and pustular psoriasis.
- Is most effective for plaque disease when combined with phototherapy.
- Decrease the dose of UVA or UVB by 50% when used in combination to avoid burning.
- Side effects are dose dependent and include elevation of triglycerides, hepatitis, hair loss, thinning of the nails, cheilitis, xerosis, and stickiness of the skin.
- Acitretin is converted to etretinate by ingestion of alcohol. Etretinate has a much longer half-life than acitretin (120 days vs. 60 hours).
- This drug is not recommended for women of childbearing potential as it is category X in pregnancy. If it is used, pregnancy should be avoided for 3 years after the last dose as the drug can be found in the body for an extended period.
- Can be used long term with minimal risk of immunosuppression.
- Baseline monitoring: CBC with diff, CMP, lipid panel.
- Maintenance monitoring of above labs every month for 3 months then every 3 months thereafter.

2. Methotrexate

- Methotrexate (MTX) is an antimetabolite that inhibits DNA synthesis.
- Is given orally or by IM administration.
- Doses begin at 7.5 to 10 mg once a week and increased by 2.5 to 5 mg per week each month until a good clinical response is seen.
- Typical maximum doses reach 20 to 25 mg once a week.
- Potential side effects include nausea, bone marrow suppression, liver toxicity, anemia, oral ulcers, and pulmonary fibrosis.

- The addition of folic acid 1 mg daily except the day the MTX is taken helps reduce nausea and counteracts the macrocytic anemia.
- Laboratory monitoring on initiation:
 1. Baseline: CBC with platelets, comprehensive metabolic panel
 2. Hep B and C serologies, pregnancy test
- Maintenance monitoring:
 1. CMP and CBC with diff every 1 to 2 months
 2. LFTs monthly for 6 months, then every 2 months
- Is category X in pregnancy, so should be used with caution and with strict birth control in women of childbearing potential.
- Can be used in combination with NBUBV phototherapy or topical therapy to improve its efficacy.
- The guidelines for liver biopsies while on chronic MTX have changed over the years. “In patients without risk factors for hepatic fibrosis, liver biopsies may not be indicated or the frequency markedly decreased” (2009 NPF consensus statement).⁷
- If MTX is being used in patients with a higher risk of hepatotoxicity, one should consider a liver biopsy after the first 2 to 6 months of therapy (to obtain a baseline), then repeat the biopsy after every 1.5 g of therapy. If possible, it is best to avoid MTX in high-risk patients.
- Risk factors for hepatic toxicity from methotrexate:
 1. History of current excessive alcohol consumption
 2. History of liver disease including chronic hepatitis B or C
 3. Persistently abnormal liver enzyme studies
 4. Lack of folate supplementation
 5. Family history of genetic liver disease
 6. History of exposure to hepatotoxic drugs
 7. Obesity
 8. Hyperlipidemia
 9. Diabetes mellitus.⁸

3. Cyclosporine A

- Cyclosporine A (CSA) causes dramatic clearing of widespread psoriasis.
 - If possible, try to use for 18 months or less at a time.
 - When to use CSA
 - i. To “rescue” a patient with a severe flare of disease
 - ii. Women of childbearing age
 - iii. Younger patients
 - iv. Patients who cannot obtain biologic medications
 - v. Used as a “bridging therapy” to transition the patient to a chronic therapy
1. Neoral is a microemulsion formula that is better absorbed; the range of dosing is 2.5 to 4 mg/kg/day divided bid.
 2. CSA selectively inhibits T-helper cell production of IL-2 while allowing an increase in suppressor T-cell populations. It has no direct effect on keratinocytes and is not a mitotic inhibitor. CSA inhibits cytokine release, which results in a decreased recruitment of APCs into the epidermis and decreases immunoreactivity of the lesions.
 3. The main potential long-term side effects are hypertension and nephrotoxicity. Glomerular filtration rate and serum creatinine should be

followed closely to evaluate renal function. If renal function is affected, the dose should be decreased or the drug discontinued.

4. Long-term use may induce interstitial fibrosis and glomerular sclerosis, so it is recommended to rotate off the CSA every 12 to 18 months.
5. Baseline monitoring: CMP, Mg, CBC with diff, U/A, lipid panel, PPD, blood pressure.
6. Monitor CMP, CBC, and blood pressure every 2 weeks while adjusting dose.
7. Maintenance monitoring every month for 3 months then every 2 to 3 months for CBC with diff, CMP, Mg, U/A, blood pressure.
8. Lipid panel every 3 to 4 months.
9. PPD yearly.
10. CSA side effects.
 - Nephrotoxicity
 - Hypertension
 - Hypomagnesemia, hyperkalemia
 - Hyperlipidemia
 - Drug interactions
 - Hypertrichosis and gingival hyperplasia
 - Increased risk of lymphoproliferative disease, especially after chronic use and with doses above 4.0 mg/kg/day

E. Biologic Therapies (Table 36-3)

- Biologic therapies were introduced in 2000 for the treatment of psoriasis and PsA. These are bioengineered molecules that target specific proteins involved in the pathogenesis of psoriasis.
- The associated table lists the biologic agents currently FDA approved and commercially available for psoriasis. The TNF- α inhibitors are also approved for PsA.
- These are indicated for patients with moderate to severe psoriasis who are candidates for systemic treatment.
- Clinical data show that these agents are highly effective at achieving significant clearing of psoriasis and have a good safety profile for long-term use.
- The TNF- α inhibitors are the only therapy available to date that can stop the progression of joint destruction in PsA.
- Some of the contraindications include guttate or pustular psoriasis; significant viral, bacterial, or fungal infections; immunosuppressed

TABLE 36-3 FDA Approved Biologic Therapies for Psoriasis

Biologic Agent	Target	Molecule
Etanercept (Enbrel)	TNF- α	Human fusion protein
Infliximab (Remicad)	TNF- α	Chimeric antibody
Adalimumab (Humira)	TNF- α	Human antibody
Ustekinumab (Stelera)	p40 subunit of IL-12/23	Human antibody

patient; past history of hepatitis B; pregnancy (TNF- α inhibitors and Ustekinumab are preg category B); malignancy within the past 5 years (not including treated basal cell carcinoma or squamous cell carcinoma); HIV infection; history of autoimmune connective tissue disease, blood dyscrasias, congestive heart failure, demyelination disorders.

- As these agents can increase the risk of activation of latent tuberculosis, a PPD skin test or IFN-gamma release assay (e.g., Quantiferon TB Gold) testing at baseline and then yearly is advised.
- Monitor CBC and CMP every 6 to 12 months.
- Patients with untreated latent tuberculosis should receive antituberculous therapy (INH) for 9 months, beginning at least 1 month before beginning the biologic.
- Live attenuated vaccines (e.g., BCG, Herpes Zoster, intranasal influenza including H1N1, MMR, rotavirus, oral polio, oral typhoid, smallpox, varicella, yellow fever) are contraindicated in patients receiving biologic therapy, so it is recommended to bring patients up to date prior to beginning therapy.

F. Potential Side Effects

- Anti-TNFs injection site reactions (in up to 20% of patients)
- Increased risk of serious infections (TB, bacterial, fungal), risk of hepatitis B reactivation, lymphoma (reported in adults, children, and adolescents)
- Increased risk of nonmelanoma skin cancer
- Congestive heart failure (new onset or exacerbation)
- Demyelinating disease (new onset or exacerbation)
- Anaphylaxis or severe allergic reactions
- Autoimmune hepatitis, cytopenias, lupus-like reaction
- New-onset palmar/plantar pustular psoriasis
- Eczematous and lichenoid skin eruptions
- Cutaneous small vessel vasculitis
- Ustekinumab injection site reactions
- Increased risk of serious infections
- Possibly associated with increased risk of cardiovascular events
- Could possibly increase risk of malignancies
- Hypersensitivity reactions (anaphylaxis, angioedema)
- Reversible posterior leukoencephalopathy syndrome (one reported case to date)

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REFERENCES

1. Gladman D. Clinical Features. In: Klippel JH, Crofford LJ, Stone JH, White PH, eds. *Primer on the Rheumatic Diseases*. 13th ed. New York: Springer; 2008:170-177.
2. Mease PJ. Treatment and Assessment. In: Klippel JH, Crofford LJ, Stone JH, White PH, eds. *Primer on the Rheumatic Diseases*. 13th ed. New York: Springer; 2009:185-192.

3. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum.* 2006;54:2665-2673.
4. Hearn RM, Kerr AC, Rahim KF, et al. Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. *Br J Dermatol.* 2008;159:931-935.
5. Van de Kerkhof P, Nestle F. Psoriasis. In: Bologna, et al., eds. *Dermatology*. 3rd ed. London: Elsevier; 2012:135-169.
6. Jackson JM, Callen JP. Immunomodulators. In: Bologna JL, Jorizzo JL, Schaffer JV, et al., eds. *Dermatology*. 3rd ed. London: Elsevier. 2012:2131-2152.
7. Kalb RE, Stober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. *J Am Acad Dermatol.* 2009;60:824-837.
8. Rosenberg P, Urwitz H, et al. Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment. *J Hepatol.* 2007;46:1111.

I. BACKGROUND Rosacea is a common and chronic inflammatory skin disease of the central face that affects at least 16 million people in the United States alone. It is characterized by two clinical components: a vascular change consisting of intermittent or persistent erythema and flushing and an acneiform eruption with papules, pustules, cysts, and sebaceous hyperplasia. Onset is most often between the ages of 30 and 50; pediatric cases have also been reported. Although women are affected three times as frequently as men, the disease may become more severe in men. Rosacea is much more common in light-skinned, fair-complexioned individuals but may also occur in darker skin types. It is estimated that 10% of individuals in Sweden have rosacea.

Etiology continues to be largely unknown. Multiple potential pathophysiologic mechanisms have been postulated, for example vascular abnormalities, dermal matrix degeneration, environmental factors, and microbial organisms, such as *Demodex folliculorum* and *Helicobacter pylori*.¹ Over recent years, however, rosacea is emerging as an inflammatory disease associated with dysregulation of the innate immune system. Through toll-like receptors (TLR) as well as other receptor families, our innate immune systems respond to environmental stimuli such as UV, microbes, and physical and chemical trauma, and release cytokines as well as antimicrobial peptides in the skin as our first line of defense. Cathelicidins, in particular LL-37 found in humans, are antimicrobial peptides that are known to be both vasoactive and proinflammatory,² exerting direct angiogenic effects on endothelium and activating innate immunity. Individuals with rosacea express abnormally elevated levels of cathelicidin³ as well as increased serine proteases,³ such as stratum corneum tryptic enzyme and kallikrein-5, compared with normal skin. These proteases lead to abnormal processing of cathelicidin, making the peptides even more proinflammatory, leading to leukocyte chemotaxis, angiogenesis, and expression of extracellular matrix components.² Injection of these abnormal cathelicidin peptides or the enzymes that produce cathelicidin into the skin of mice leads to skin inflammation characteristic of the pathologic changes in rosacea.³ Further support of dysfunction of the innate immune system as a central cause of rosacea recently came again from Yamasaki et al.,⁴ revealing that, unlike other inflammatory skin disorders, the epidermis of patients with rosacea express higher levels of toll-like receptor 2 (TLR-2) compared to normal. Overexpression of TLR-2 then stimulates increased serine protease activity by keratinocytes,⁴ leading to higher levels of cathelicidin. While more research needs to be performed to better explain the etiology of rosacea, it appears promising that rosacea is linked to a defect in innate immunity. The facial lesions of rosacea often cause justifiable concern about personal appearance, and patients will frequently seek the care of various medical providers to help with treatment. The diagnosis of rosacea is made by fulfilling one of several primary and one of many secondary

criteria. Primary criteria for rosacea include transient erythema/flushing, persistent facial redness, papules and pustules, and increased facial telangiectasias. Secondary criteria include burning/stinging, elevated red facial plaques with or without scale, dry/scaly skin, persistent facial edema (subtypes of solid facial or soft facial type), phymatous changes, and ocular manifestations such as burning/itching, conjunctival hyperemia, lid inflammation, styes, chalazia, and corneal damage.

II. CLINICAL PRESENTATION There are four subtypes of rosacea that have been defined by the National Rosacea Society Committee⁵ on the classification and staging of rosacea: (A) erythematotelangiectatic, (B) papulopustular, (C) phymatous, and (D) ocular.

- A.** Erythematotelangiectatic rosacea (Fig. 37-1) is characterized by prolonged flushing and persistent central facial erythema with or without telangiectasia. Periocular skin is characteristically spared. Patients typically experience a burning or stinging sensation, which may be exacerbated by topically applied products.
- B.** The papulopustular type (Fig. 37-2) has persistent central facial erythema and transient acneiform papules, pustules, and cysts. Unlike acne, comedones



Figure 37-1. Erythematotelangiectatic rosacea: Background erythema with fine telangiectasias of the central face. Note the lack of inflammatory lesions. (Image provided by Stedman's.)



Figure 37-2. Papulopustular rosacea: Inflammatory papules and pustules on a background of erythema and fine telangiectasia of the central face. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

are not present. Inflammatory lesions may be painful. Chronic facial edema may follow repeated episodes of inflammation. In addition to the face, the lesions of rosacea may be seen on the neck, scalp, shoulders, and upper back.

- C. Phymatous rosacea (Fig. 37-3) occurs most often on the nose (rhinophyma) and is characterized by thick skin with an irregular surface, nodularities, and bulbous enlargement. Rhinophyma predominantly affects men. Careful evaluation of a nose with the changes of rhinophyma should be undertaken because basal cell carcinomas may be present, as well as less common tumors. Pseudorhinophyma can be seen when heavy eyeglasses obstruct the lymphatic and venous drainage from the nose.
- D. In ocular rosacea (Fig. 37-4), blepharitis and conjunctivitis are the most common findings. Ocular complaints include stinging, photophobia, burning, tearing, scratchiness, and a sense of a foreign body being in the eye. Patients may also have a history of recurrent chalazion. Rarely, keratitis may lead to blindness. Ocular rosacea may precede the cutaneous findings by many years, but the frequency of ocular symptoms increases as rosacea progresses. The severity of the eye involvement does not correlate with the severity of facial involvement. Ocular symptoms can often be elicited on the routine investigation of rosacea patients, as more than 50% of rosacea patients will have ocular involvement.

The National Rosacea Society Expert Committee⁵ further classifies granulomatous rosacea as a disease variant characterized by noninflammatory, hard, brown, yellow, or red papules/nodules of the central face. It is of note that rosacea fulminans (pyoderma faciale), steroid-induced acneiform eruption, and perioral dermatitis are not considered rosacea variants but separate entities.



Figure 37-3. Mixed rosacea: A mix of the subtypes of rosacea with evidence of rhinophyma, inflammatory papules, pustules, and background erythema, along with severe blepharitis. (From Tasman W, Jaeger E. *The Wills Eye Hospital Atlas of Clinical Ophthalmology*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.)



Figure 37-4. Ocular rosacea: Inflammation of the eyes (conjunctivitis) and lids. This patient also has inflammatory papules and pustules of rosacea on the face. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

III. WORKUP The diagnosis of rosacea is a clinical one, and no benchmark laboratory test exists. Differential diagnostic considerations include (i) acne vulgaris, which is characterized by a wider distribution of lesions and the presence of comedones, (ii) periorificial dermatitis, (iii) seborrheic dermatitis, (iv) contact dermatitis, (v) malignant carcinoid syndrome, (vi) lupus erythematosus, and (vii) photodermatoses. Other exclusions are medications and topical products. Drugs associated with flushing include vasodilators, calcium channel blockers, cholinergic agents, opiates, cyclosporin, nicotinic acid, tamoxifen, and rifampin. Topical sorbic acid, a common component of cosmetics and corticosteroids, can cause facial redness and itching.

IV. TREATMENT

A. Precipitating Factors. Patients who flush easily should avoid hot food and drinks and activities that induce this change. These may include tea, coffee, sunlight, extremes of heat and cold, and emotional stress. It has been demonstrated that the flushing caused by coffee is induced by a temperature of 60°C and above, but not by cold coffee or caffeine alone. Other triggers include alcohol, spicy foods, and exercise. A printed handout with trigger factors is helpful for the individual patient to identify any causative agents for worsening of their rosacea symptoms. If flushing is not caused by these factors, there is no evidence that avoidance will result in improvement of the disease. Vasodilator drugs that affect peripheral blood vessels will also exacerbate rosacea flushing. The vascular reactivity of rosacea flushing may be confused with menopausal flushing and carcinoid flushing.

B. Topical Therapy

1. Topical metronidazole (0.75% cream or gel; 1% gel, lotion, and cream) is an imidazole antibiotic that is thought to have antioxidant effects to protect against neutrophilic-derived reaction oxygen species (Table 37-1). In various placebo-controlled, randomized, double-blinded studies, topical metronidazole demonstrated efficacious treatment in moderate-to-severe rosacea patients. A once-daily application of metronidazole 1% gel was shown to decrease inflammatory lesions by 77% over a 15-week period.⁶ The gel formulation has a higher rate of penetration based on *in vitro* studies. Typical adverse events have included mild skin reactions, such as stinging, burning, scaling, and dryness.
2. Topical azelaic acid (15% gel) is an alternative, or adjunctive therapy in rosacea patients with a low-side effect profile. The proposed mechanism of action is presumably by the reduction of proinflammatory reactive oxygen species. Use of azelaic acid 15% gel twice daily decreased inflammatory rosacea lesions by 80%.⁶ Local skin reactions, including facial burning, stinging, and pruritus, were reported among the adverse events, and were typically mild to moderate in intensity.
3. Preparations containing sodium sulfacetamide 10% and sulfur 5% (available as lotion, cream, gel, or cleanser) are helpful. Sulfacetamide has antibacterial properties, and sulfur is antifungal, antiodemectic, and has keratolytic effects. These preparations may have an unpleasant odor. However, recent formulations have successfully concealed the unappealing odor. Patients with sulfa allergies should avoid these products.

TABLE 37-1 **Top Treatment Choices for Rosacea****Oral agents**

Tetracycline	250–500 mg b.i.d.-q.i.d.
Doxycycline	40 mg q.d. up to 100 mg b.i.d.
Minocycline	100 mg b.i.d.

Topical agents

Metronidazole	0.75–1% cream, gel, or lotion q.d.-b.i.d.
Azelaic acid	15% gel b.i.d.
Sodium sulfacetamide and sulfur	10/5% lotion, cream, gel, or cleanser q.d.-b.i.d.

4. Topical erythromycin or clindamycin lotions may be used b.i.d., as in the treatment of acne vulgaris. Recently, a pilot study was conducted to assess the efficacy and safety of a clindamycin phosphate 1.2% and tretinoin 0.025% combination gel for the treatment of papulopustular rosacea. While there was no statistically significant improvement in papule/pustule count between treated and placebo groups, the data suggested that the combination may improve the telangiectatic component of rosacea.⁷ The authors concluded that future studies are warranted, but need to be larger in sample size.
5. Topical retinoids (tretinoin, tazarotene, and adapalene) have also been reported to be used in the treatment of rosacea. There is scant evidence in the literature to support its use, and moreover it is not approved for the rosacea indication.
6. Topical corticosteroids are occasionally used to decrease erythema and inflammation, and should be reserved for short-term treatment of severe inflammatory rosacea. The high-potency corticosteroid preparations should never be used because they may induce more widespread and irreversible telangiectasias. Use of 1% hydrocortisone is acceptable for short-term use.
7. α -Adrenergic receptor agonists have been shown to effectively treat the diffuse facial erythema that is associated with rosacea. Topical brimonidine tartrate 0.33% gel received recent approval by the FDA for approval to use in patients with facial erythema of rosacea. Brimonidine tartrate is a highly selective agonist for the α -2-adrenergic receptor, and its mechanism of action is vasoconstriction of small distal resistance arteries by way of postsynaptic α -2-adrenergic receptor signaling on the vascular smooth muscle. Two, randomized, double-blind, vehicle controlled, phase II studies have recently demonstrated the efficacy and safety of the once-daily dosing of the brimonidine tartrate gel in adult subjects with moderate to severe facial erythema of rosacea.⁸ Reduction of erythema for the brimonidine tartrate gel occurred within 30 minutes, with a

peak effect lasting approximately 4 to 6 hours, and erythema returned to baseline levels at a final 12-hour time point. Rebound, which is defined as a score worse than baseline measurements, was not observed. Neither tachyphylaxis, nor worsening of inflammatory lesion counts or severity of telangiectasias was observed. Taken further, the data from the phase II study reveal that there was no adverse effect on blood pressure, heart rate, intraocular pressure, and skin tolerability, and suggest that brimonidine tartrate gel is safe and well tolerated at the various concentrations, and application frequencies.

Another adrenergic receptor agonist, oxymetazoline, has also been shown to reduce facial erythema in adult patients with erythotelangiectatic rosacea (ETR)⁹ based on a case-report study. Unlike brimonidine tartrate, oxymetazoline is selective for α -1-adrenergic receptor, and causes vasoconstriction on peripheral cutaneous arterial vessels.

8. Ultraviolet light therapy is of no benefit, and may worsen symptoms.
9. Photodynamic therapy (PDT) appears to be effective in rosacea patients treated with topical methylaminolevulinate (MAL) or 5-aminolevulinic acid (5-ALA). The purported rationale for using PDT is to alter the local skin microbiome either by immunosuppressive effects, or through inhibition of bacterial growth via endobacterial porphyrins.

C. Systemic Therapy

1. Tetracyclines and its second-generation derivatives (doxycycline and minocycline) have long since been used as the primary treatment for rosacea. For tetracycline, therapy is usually initiated at 250 mg q.d. until symptoms subside, but dosages can range from 200 to 500 mg, once or twice daily, and can be decreased slowly or discontinued. As for doxycycline and minocycline, dosages range between 100 to 200 mg per day and 50 to 100 mg per day, respectively, and can also be tapered. While antibiotic-level dosing of tetracyclines has been shown to be effective as initial and maintenance treatment, there are some drawbacks. Nausea/gastrointestinal upset is a significant side effect of tetracycline therapy. But most importantly, prolonged antibiotic usage may alter endogenous microflora, and trigger the development of antibiotic-resistant strains. It must be noted, however, that there is still a need for a better understanding of the true effect that antibiotic therapy has on bacterial resistance.¹⁰

After discontinuing tetracycline therapy, 25% of patients can be expected to relapse within a few days; approximately 60% will have a relapse within 6 months. Keratitis always seems to recur quickly and may require continual treatment. Ocular rosacea responds to oral tetracyclines or erythromycin. Higher doses may be required initially and then doses as little as 250 mg q.d. or q.o.d. of either antibiotic may be sufficient. Long-term remissions may occur, requiring episodic oral therapy.

2. Doxycycline 40 mg capsules (30 mg immediate/10 mg delayed release doxycycline monohydrate beads) are the only FDA-approved subantimicrobial dose doxycycline indicated for the effective treatment of inflammatory lesions associated with rosacea (ref). Based on the pivotal studies for FDA approval, the mean reduction of total inflammatory lesions in the active (doxycycline 40 mg) arm was significantly greater than the placebo arm.¹¹ The incidences of gastrointestinal side effects are also minimal as compared to conventional antibiotic dosages of doxycycline.

The modified release doxycycline capsules were designed to specifically target and inhibit matrix metalloproteinases, which are central in rosacea's pathophysiology.¹²

It must be noted that the doxycycline 40 mg capsules were designed to confer anti-inflammatory activity, and should not be used to combat bacterial infections. Furthermore, treatment with subantimicrobial dose doxycycline has not been shown to correlate with the development of antibiotic resistant organisms.¹³

3. Oral metronidazole has been reported to be an effective alternative to oral tetracyclines. Oral metronidazole at 200 mg b.i.d. exhibited equivalent decreases in papules and pustules counts as compared to oxy-tetracycline.¹⁴ Patients must be forewarned of its disulfiram (Antabuse)-like side effects if alcohol is consumed during treatment, as well as an associated peripheral neuropathy with prolonged use.
4. Ampicillin (250 mg b.i.d. to t.i.d.) has also been shown to be useful.
5. Trimethoprim/sulfamethoxazole on a daily basis has a rapid onset of action but has rare associated side effects of bone marrow suppression and toxic epidermal necrolysis (TEN).
6. Clarithromycin (Biaxin) in a dose of 250 mg b.i.d. for 4 weeks and then 250 mg q.d. for 4 weeks is another oral alternative for treatment-resistant patients.
7. Azithromycin as low as 250 mg three times weekly has been another effective regimen.
8. Menopause-related flushing or intractable flushing might respond to low doses of clonidine, for menopausal flushing (Catapres), an α -adrenergic agonist, at a dose of 0.05 mg PO b.i.d. or through a transdermal patch. It is otherwise apparently ineffective in rosacea.
9. Isotretinoin (0.5 mg/kg/day for 20 weeks) can be highly effective in patients with severe refractory papulopustular rosacea. There is improvement in edema, erythema, and telangiectasias and a decrease in sebaceous gland hyperplasia, rhinophyma, and oily skin. Ocular side effects of therapy occur more frequently than with acne. One study showed efficacy with as little as 10 mg per day of isotretinoin for 16 weeks. Other dosing regimens include 10 mg two to three times per week or 20 mg two times per week. Remission rates remain to be determined, but some patients note prolonged disappearance of disease. Patients with rosacea are generally older than those with acne, and even more care concerning adverse effects is necessary when using retinoid drugs.
10. Oral spironolactone at 50 mg per day for 4 weeks improved rosacea in 11 of the 13 patients studied. The improvement was hypothesized to be secondary to changes in the metabolism of sex steroid hormones.
11. Rosacea-like demodicidosis can be treated with oral ivermectin (200 μ g/kg) and/or topical permethrin cream.
- D. Telangiectatic vessels may be destroyed by multiple vascular lasers such as the long pulsed-dye laser (585 to 600 nm), the KTP laser (532 nm), or an intense pulsed light source. Several treatments may be required with each system. Pinpoint electrosurgery using the epilating needle is also an option but carries an increased risk of scarring when compared with current laser options. In one study, the pulsed-dye laser also reduced the number of papules and pustules by 60%; the intense pulsed light

source is also being used to treat both the inflammatory and vascular components of rosacea.

- E. Ocular rosacea with associated blepharitis can be treated with topical antibiotic bacitracin/polymyxin B. The lid margins can be gently scrubbed with baby shampoo on a cotton-tipped applicator, commercially available lid scrubs, or a nonabrasive gauze pad impregnated with a surfactant cleanser. Warm compresses q.i.d. are helpful in removing adherent crusts. If significant inflammation is present, a topical steroid ointment can be applied to the eyelid margins on only a short-term basis.

Subantimicrobial dose doxycycline was shown to be effective in long-term therapy for ocular rosacea based on the results from a retrospective study.¹⁵

- F. Surgical reduction of the soft tissue enlargement in rhinophyma may be accomplished by CO₂ laser surgery, a surgical shave, dermabrasion, or electrosurgery.
- G. Cosmetic lotions and foundations with a green tint help to camouflage the redness and telangiectasias of rosacea.
- H. Use of mild nonsoap cleansers as well as a SPF 15 sunscreen that protects against ultraviolet A (UVA) and UVB is recommended on a daily basis. Products containing zinc and titanium dioxide are tolerated the best. To minimize irritation, 30 minutes should elapse after washing before applying topical products. Cool compresses, gel masks, sucking of ice chips, central facial massage, biofeedback, and flaxseed oil are all nonstudied alternative therapies.
- I. A list of multiple foods is available to determine what items may be trigger factors for rosacea. The National Rosacea Society is an excellent general resource for both patients and providers at 1-888-662-5874 or www.rosacea.org.

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REFERENCES

1. Elewski BE, Draelos Z, Dreno B, et al. Rosacea—global diversity and optimized outcome: proposed international consensus from the Rosacea International Expert Group. *JEADV*. 2011;25:188-200.
2. Yamasaki K, Gallo RL. The molecular pathology of rosacea. *J Dermatol Sci*. 2009;55:77-81.
3. Yamasaki K, Di Nardo A, Bardan A, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med*. 2007;13:975-980.
4. Yamasaki K, Kanada K, Macleod DT, et al. TLR2 expression is increased in rosacea and stimulates enhanced serine protease production by keratinocytes. *J Invest Dermatol*. 2011;131:688-697.
5. Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *J Am Acad Dermatol*. 2002;46:584-587.
6. Wolf JE, Kerrouche N, Arsonnaud S. Efficacy and safety of once-daily Metronidazole 1% gel compared with twice-daily azelaic acid 15% gel in the treatment of rosacea. *Cutis*. 2006;77:3.

7. Chang AL, Alora-Palli M, Lima XT, et al. A randomized, double-blind, placebo-controlled, pilot study to assess the efficacy and safety of clindamycin 1.2% and tretinoin 0.025% combination gel for the treatment of acne rosacea over 12 weeks. *J Drugs Dermatol*. 2012;11(3):333-339.
8. Fowler J, Jarratt M, Moore A, et al. Once-daily topical brimonidine tartrate gel 0.5% is a novel treatment of moderate to severe facial erythema of rosacea: results of two multicenter, randomized and vehicle controlled studies. *Br J Dermatol*. 2012;166:633-641.
9. Shanler SD, Ondo AL. A successful treatment of erythema and flushing of rosacea using a topically applied selective alpha1-adrenergic receptor antagonist, oxymetazoline. *Arch Dermatol*. 2007;143:1369-1371.
10. Thiboutot D. Dermatologists do not yet fully understand the clinical significance of antibiotic use and bacterial resistance in patients with acne: comment on "Antibiotics, acne, and *Staphylococcus aureus* colonization." *Arch Dermatol*. 2011;147(8):921-922.
11. Del Rosso JQ, Webster GF, Jackson M, et al. Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg doxycycline, USP capsules) administered once daily for treatment of rosacea. *J Am Acad Dermatol*. 2007;56:791-802.
12. Gu Y, Walker C, Ryan ME, et al. Non-antibacterial tetracycline formulations: clinical applications in dentistry and medicine. *J Oral Microbiol*. 2012;4:19227.
13. Berman B, Perez O, Zell D. Update on rosacea and anti-inflammatory dose doxycycline. *Drugs Today (Barc)*. 2007;43:27-34.
14. Pye RJ, Burton JL. Treatment of rosacea by metronidazole. *Lancet*. 1976;1(7971):1211-1212.
15. Pfeffer I, Borelli C, Zierhut M, et al. Treatment of ocular rosacea with 40 mg doxycycline in a slow release form. *J Dtsch Dermatol Ges*. 2011;9(11):904-907.

I. BACKGROUND Seborrheic dermatitis and dandruff are common, chronic, relapsing, scaling disorders which share a similar origin. Seborrheic dermatitis is thought to affect up to 5% of the general population, and its milder counterpart, dandruff, has been said to affect up to 50% of the population.^{1,2} When compared to patients with a normal scalp, patients with seborrheic dermatitis or dandruff have an increased number of nucleated cells/cm² (6.8× for dandruff; 20.5× for seborrheic dermatitis) and lose a higher number of cells/cm² after hair washing. Dandruff is a noninflammatory, mild form of seborrheic dermatitis of the scalp caused by excessive physiologic desquamation. In comparison, seborrheic dermatitis is an inflammatory, erythematous, scaling eruption in areas of the skin with a high number of sebaceous glands.

The exact cause of seborrheic dermatitis is unknown, but its etiology is believed to be multifactorial. Sebum production, the presence of and the immune response to certain *Malassezia* (previously *Pityrosporum*) yeast species (most commonly *Malassezia globosa* and *Malassezia restricta*), atmospheric humidity, and stress may all be contributing factors. Although seborrheic dermatitis and dandruff occur in areas with a high density of sebaceous glands, there is no direct correlation between sebum production and the presence or activity of disease. Furthermore, reducing the amount sebum production does not eliminate dandruff or seborrheic dermatitis. In contrast, a reduction in the number of *Malassezia* yeast after treatment with antifungals has been shown to improve seborrhea. *Malassezia* may contribute to the inflammation found in seborrheic dermatitis by the yeast's lipase activity, the toxic metabolites they produce, and the abnormal immune response they create. *Malassezia* increases the number of natural killer cells and inflammatory interleukins by activating the complement pathways (classic and alternative).

Seborrheic dermatitis has a familial tendency and is found with increased incidence in a variety of medical conditions, including Parkinson disease, other neurologic disorders, HIV/AIDS, depression, other mood disorders, and tinea versicolor (Table 38-1). The incidence of seborrheic dermatitis has been reported to be as high as 30% to 83% in patients with HIV/AIDS.^{1,2} An increased incidence of seborrhea has also been found in patients with a personal or family history of atopic dermatitis.

II. CLINICAL PRESENTATION Seborrheic dermatitis typically occurs during infancy, puberty, and in adults aged greater than 50 years, with males affected more often than females. Seborrheic dermatitis and dandruff have a mild clinical course. The lesions tend to be asymptomatic or mildly pruritic (seborrheic dermatitis worse than dandruff), with episodic exacerbations associated with cold weather, stress, and infection. The lesions of dandruff appear as nonerythematous,

TABLE 38-1 **Differential Diagnosis**

- Atopic dermatitis
- Rosacea
- Psoriasis
- Impetigo
- Tinea infection (capitis, cruris, corporis)
- Tinea versicolor
- Acne vulgaris
- Irritant contact dermatitis
- Allergic contact dermatitis
- Drug eruption
- Systemic lupus erythematosus
- Langerhans cell histiocytosis
- Other dermatophytoses

noninflammatory, white, or greasy scaling throughout the scalp (Fig. 38-1). The lesions of seborrheic dermatitis appear as erythematous, inflammatory, greasy, yellow to brown scaling patches or plaques affecting the scalp, face (eyebrows, eyelids, nasal alar crease, mouth, and ears), and body (central chest and genital region in adults, diaper region in infants) (Figs. 38-2 and 38-3).

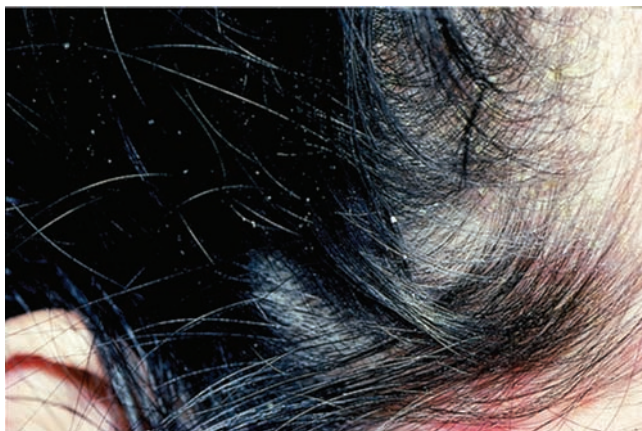


Figure 38-1. Dandruff. Note scaling with very little inflammation. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 38-2. Seborrheic dermatitis involving the cheeks and nasolabial folds. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 38-3. Seborrheic dermatitis on chest. (McConnell TH. *The Nature of Disease Pathology for the Health Professions*. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.)

Seborrheic dermatitis of the scalp typically presents with ill-defined patches on the crown and parietal regions of the scalp and anterior hairline. Facial seborrheic dermatitis often presents with dry, mildly erythematous, scaling patches that can progress to thick, greasy, exudative areas which may become infected if left untreated. When confined to the area around the eyelids (seborrheic marginal blepharitis), seborrheic dermatitis may be associated with ocular rosacea

or mild conjunctivitis (Fig. 38-4). Seborrheic dermatitis can occasionally produce thick, discoid plaques (medallion lesions).¹ Infantile seborrheic dermatitis typically involves the vertex of the scalp (cradle cap), flexural surfaces, and diaper region (Fig. 38-5). Pruritus is not as common in infants and the disease is oftentimes self-limited, with presentation in the first few months of life and resolution by 1 year.¹



Figure 38-4. Seborrheic blepharitis. Note the concurrent facial seborrheic dermatitis. (Berg D, Worzala K. *Atlas of Adult Physical Diagnosis*. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)



Figure 38-5. Cradle cap. (From Fleisher GR, Ludwig S, Baskin MN. *Atlas of Pediatric Emergency Medicine*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

III. WORKUP The diagnosis of seborrheic dermatitis is usually made based on history and physical examination alone (Table 38-2). A negative KOH test will rule out tinea and candidiasis. Rarely, biopsy may be needed to confirm the diagnosis or rule out other conditions that may mimic seborrheic dermatitis, including atopic dermatitis, psoriasis, rosacea, impetigo, tinea infection (capitis, corporis, or cruris), tinea versicolor, acne vulgaris, irritant contact dermatitis, and allergic contact dermatitis.² Histology shows retention of nuclei in the cells of the stratum corneum due to accelerated epidermal growth and the inability to complete maturation. It may be necessary to review the patient's medications, as drug reactions to a variety of medications, including gold, methyldopa, chlorpromazine, or cimetidine therapy, and vitamin B deficiency can mimic seborrheic dermatitis. Given the increased incidence of disease association with HIV/AIDS, patients who present with extensive, generalized seborrheic dermatitis should be tested for HIV.

IV. TREATMENT Treatment for seborrheic dermatitis and dandruff is focused on eliminating the visible disease (scale and erythema) and symptomatic relief (especially pruritus) through the use of antifungal, antiinflammatory, and keratolytic agents (Table 38-3).

A. Antifungals. Topical antifungals are considered first-line medications for the treatment of seborrheic dermatitis. Topical ketoconazole is a safe, effective, and well-tolerated treatment for seborrheic dermatitis, with minimal to no systemic absorption. Ketoconazole is available as a 2% shampoo (Nizoral) or 2% foam (Extina) for scalp seborrheic dermatitis and a 2% cream (Nizoral) or 2% gel (Xolegel) for nonscalp seborrheic dermatitis. Ketoconazole 2% shampoo is used twice weekly and left on for 5 to 10 minutes prior to rinsing for approximately 4 weeks, followed by a weekly maintenance application. Ketoconazole 2% foam is applied to the scalp and left on overnight. For nonscalp seborrheic dermatitis, ketoconazole 2% cream (Nizoral) or 2% gel (Xolegel) applied twice daily for 4 weeks is effective.

TABLE 38-2	Laboratory Workup
Biopsy	
KOH	
HIV testing (if appropriate)	

TABLE 38-3	Primary Treatment Options
1. Antifungals (ketoconazole, ciclopirox)	
2. Topical Corticosteroids (betamethasone, desonide, clobetasol)	
3. Keratolytics (selenium sulfide, zinc pyrithione, tar shampoo, salicylic acid)	
4. Calcineurin Inhibitors (pimecrolimus, tacrolimus)	

Ciclopirox is another antifungal agent found to be safe, effective, and well tolerated. Ciclopirox 1% shampoo (Loprox) is used twice weekly for 4 weeks, and ciclopirox 1% cream (Loprox) is applied twice daily for 1 month followed by daily application for maintenance. Although preparations containing either 2% ketoconazole or 1% ciclopirox are effective as monotherapy, more severe or very inflammatory cases may require combination therapy with topical corticosteroids. Furthermore, a short course (1 to 2 weeks) of topical corticosteroids may be more effective for severe cases of seborrheic dermatitis.

Other antifungals found to be effective against seborrheic dermatitis include miconazole 2% cream (Micatin), terbinafine 1% solution or 1% cream (Lamisil), and fluconazole. Although infantile seborrheic dermatitis is usually self-limited, bifonazole 1% shampoo is both safe and effective in infants, should treatment be necessary. There are limited data on the effectiveness of oral antifungals.¹ A nonsteroidal cream with no active ingredients has shown anti-inflammatory and antifungal activity (Promiseb), gaining the Food and Drug Administration (FDA) approval for the treatment of seborrheic dermatitis.

B. Topical Corticosteroids. Topical corticosteroids are considered either first- or second-line agents in the treatment of seborrheic dermatitis. They are inexpensive and effective at rapidly decreasing the inflammation and pruritus associated with seborrheic dermatitis. Low to mid-potency corticosteroids treat most cases of seborrheic dermatitis, but higher potency steroids followed by a taper may be necessary to treat refractory scalp seborrheic dermatitis. High-potency steroids should be avoided on the face. Due to the potential side effects, including skin atrophy, telangiectasia formation, and glaucoma or cataracts (with use near the eyes), treatment with topical steroids should be limited to a few weeks.

Nonscalp seborrheic dermatitis can be treated with over-the-counter hydrocortisone 1% cream applied one to three times daily for a few weeks at a time. Refractory or extensive lesions on the scalp may be treated with corticosteroid lotions, solutions, sprays, or foam. Formulations include betamethasone valerate 0.1% lotion (Valisone) or cream (Beta-Val), betamethasone valerate 0.12% foam (Luxiq), betamethasone dipropionate 0.05% cream (Diprosone) or ointment (Diprolene), desonide 0.05% gel (Desonate), desonide 0.05% cream, lotion or ointment (DesOwen), and clobetasol propionate 0.05% foam (Olux, Olux-E) or solution. Fluocinolone acetonide 0.01T scalp oil (Derma-Smoother) usually used with occlusion is another effective treatment.

C. Topical Calcineurin Inhibitors. The calcineurin inhibitors, tacrolimus 0.03%, 0.01% ointment (Protopic), and pimecrolimus 1% cream (Elidel), are immunomodulators that decrease inflammation by inhibiting T-cell function. Twice daily application of pimecrolimus cream may be as effective at treating moderate-to-severe seborrheic dermatitis as antifungals and corticosteroids without the side effect profile of prolonged corticosteroid use. FDA has warned against a potential increased risk of skin cancer and lymphoma after extensive, widespread use of calcineurin inhibitors.^{1,2} As such, antifungals remain the first-line treatment.

D. Other Nonsteroidals. Preparations containing 2.5% selenium sulfide (Selsun) or 1% to 2% zinc pyrithione (Danex, DHS Zinc, Head & Shoulders, Zincon) are also effective at treating seborrheic dermatitis. Selenium sulfide has both antimetabolic and antifungal properties. Zinc pyrithione has cytotoxic, antimicrobial, and antifungal properties. Application

of the selenium sulfide 2% shampoo three times weekly for a treatment period of 5 to 10 minutes is nearly as effective as ketoconazole in treating seborrheic dermatitis. Unfortunately, it is less effective at preventing relapse of disease.¹ Tar shampoos (DHS-T, Ionil T, Pentrax, Sebutone, T/Gel, Zetar), like selenium sulfide containing shampoos, inhibit mitotic activity, thus decreasing the amount of scale. Salicylic acid disrupts the bonds between cells within the stratum corneum. However, this product has not been well studied in adults and salicylic acid/sulfur shampoos (Ionil, Sebulex) are less effective than other keratolytics.¹ Hair discoloration is one of the major side effects of both selenium sulfide and tar shampoos. Overnight application of keratolytic gel or a 30-minute application of warm mineral oil prior to shampooing may help remove thick crusts.

In patients suffering from both facial seborrheic dermatitis and rosacea, metronidazole 0.75% or 1% gel (MetroGel) and azelaic acid 15% gel (Finacea) are safe, well tolerated, and effective.^{1,2} Metronidazole 1% gel is typically applied once daily at bedtime, and azelaic acid gel is applied once to twice daily.

ACKNOWLEDGMENT

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REFERENCES

1. Del Rosso JS. Adult seborrheic dermatitis: a status report on practical topical management. *J Clin Aesthet Dermatol.* 2011;4(5):32-38.
2. Bikowski J. Facial seborrheic dermatitis: a report on current status and therapeutic horizons. *J Drugs Dermatol.* 2009;8(2):125-133.

Suggested Readings

- Naldi L, Rebora A. Clinical practice: seborrheic dermatitis. *N Engl J Med.* 2009;360(4):387-396.
- Sampaio AL, Mameri AC, Vargas TJ, et al. Seborrheic dermatitis. *An Bras Dermatol.* 2011;86(6):1061-1071.
- Schmidt JA. Seborrheic dermatitis: a clinical practice snapshot. *Nurse Pract.* 2011;36(8)32-37.

I. BACKGROUND Seborrheic keratoses (SKs) are common benign epidermal tumors found in middle-aged and elderly populations. The term “seborrheic” refers to the lesion’s greasy appearance and location in areas that have many sebaceous glands. However, there is no known relationship to sebaceous gland function, seborrhea, or seborrheic dermatitis. The cause of SKs is unknown. Genetics (polygenic), sun exposure, and infection are all implicated as possible predispositions to developing SKs. In mature SKs, deoxyribonucleic acid (DNA) synthesis is decreased, while ribonucleic acid and protein synthesis is increased with irregularities in the expression patterns of apoptosis markers. Many patients with SKs have positive family history for the condition, but validated studies are lacking. Sun exposure has been shown to increase the prevalence of SKs, but there are some studies disagreeing with the role of genetics in SK development. Viral infection has also been explored as a possible cause of SKs. SKs from the genital region may contain human papillomavirus (HPV) DNA, but the role of HPV in developing SKs has been controversial. A recent study reported that HPV-positive genital SKs arise in younger, sexually active age groups.

While concern about these lesions is primarily cosmetic, some lesions with multiple dark colors raise the question of melanoma. Rarely, malignant lesions (i.e., basal cell carcinoma [BCC] and squamous cell carcinoma [SCC]) can arise within SKs, especially the reticulated type on sun-damaged skin. In a retrospective study of 813 histologically diagnosed SKs, 5.3% were associated with nonmelanoma skin cancer. No melanomas were observed. The most common malignancy was Bowen disease, followed by BCC, then invasive SCC.

II. CLINICAL PRESENTATION SKs are generally asymptomatic. Irritated lesions or those in intertriginous areas may cause intense pruritus. SKs start as small flesh-colored, yellow, or tan-colored waxy papules that may grow to become dark brown or black greasy verrucous lesions with a distinct border (Fig. 39-1). The rough scale may sometimes flake or be rubbed off but will regrow. The keratoses appear to be “stuck on” the skin (Fig. 39-2), and close inspection with a hand lens will expose the presence of horn cysts or dark keratin plugs. Stucco keratosis, a variant of SKs, is 1- to 5-mm lightly colored keratotic papules on the dorsa of the hands and feet and lower legs. A variant of SKs known as dermatosis papulosa nigra is seen primarily on the cheeks in blacks or other dark-skinned individuals with a familial predisposition. These lesions are small, pigmented papules that may be pedunculated.



Figure 39-1. Seborrheic keratosis with “stuck-on” appearance. (From Goodheart HP. *Goodheart’s Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 39-2. Multiple seborrheic keratoses on the back. (From Goodheart HP. *Goodheart’s Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

III. WORKUP Any rapidly growing, symptomatic, atypical lesions should be pathologically examined, and the base of all cutaneous horns submitted to rule out any malignancies such as nonmelanoma skin cancer or melanoma. Shave biopsies or curettage specimens are often not sufficient for definitive histologic diagnosis. Please see Table 39-1 for differential diagnoses.

TABLE 39-1 Differential Diagnosis

1. Actinic keratosis
2. Basal cell carcinoma
3. Bowen disease
4. Bowenoid papulosis
5. Cutaneous horn
6. Epidermodysplasia verruciformis
7. Lentigo
8. Melanoma
9. Nevus sebaceous
10. Psoriasis (guttate or plaque)
11. Squamous cell carcinoma
12. Stucco keratosis
13. Warts

The development of multiple SKs has been attributed to estrogen therapy, preexisting inflammatory dermatoses, chemotherapy (especially cytarabine), and various internal malignancies. The latter association (Leser-Trélat sign), although somewhat controversial, should at least arouse one's suspicion when multiple eruptive SKs arise rapidly in association with skin tags and acanthosis nigricans. Adenocarcinoma of the stomach or lung is the most commonly associated malignancy with the sign of Leser-Trélat sign.

IV. TREATMENT SKs are benign lesions but may be symptomatic with pruritus or bleeding. Any destructive modality may be used to treat these lesions. However, the patient must be warned that destructive treatments may lead to scarring, hypopigmentation, or recurrence (Table 39-2).

A. Cryosurgical Application of liquid nitrogen for 15 to 20 seconds is generally the simplest method of destruction. Multiple areas can be treated easily without anesthesia.

B. Simple Curettage, with or without anesthesia, leaves an excellent cosmetic result. Lesions lightly frozen with a refrigerant, CO₂, or liquid nitrogen may sometimes be scraped off more easily. Monsel solution (ferric subsulfate), ferric chloride, aluminum chloride, Gelfoam, weak acids (30% trichloroacetic), or pressure may be used for hemostasis. Light electrodesiccation will accomplish the same end but may induce a small scar. Lesions should remain uncovered or have only a light ointment applied such as Aquaphor Healing Ointment.

C. Very Thick or Pedunculated SKs may be best removed with a shave excision or with sharp scissors. For lesions with a possibility of malignancy, removal should be done to yield a pathology sample.

TABLE 39-2	Primary Treatment Options
<ol style="list-style-type: none">1. Cryotherapy2. Cryotherapy with curettage3. Shave excision after anesthesia4. Electrodesiccation5. Laser ablation	

- D. Lesions of Dermatosi Papulosa Nigra** are best treated by simple curet-
tage but may also be treated by Gradle scissor excision, very light electro-
surgery, laser surgery, or cryosurgery. It is particularly important not to treat
too aggressively so as to avoid posttreatment hypopigmentation, especially
in darker skin patients.
- E. Ammonium Lactate 12% Lotion** (Lac-Hydrin) applied b.i.d. for 1 to
2 months may reduce the height of SKs but will not change the width or
color of the lesions.
- F. SKs** have also been managed with laser treatments such as 532-nm diode
lasers with color enhancement using a red marker or ferric subsulfate. In
a study of 326 patients with SKs, 93% of the lesions were resolved com-
pletely without any hyperpigmentation or hypertrophic scar formation
following laser treatment.

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Suggested Readings

Culbertson GR. 532-nm diode laser treatment of seborrheic keratoses with color enhance-
ment. *Dermatol Surg.* 2008;34(4):525-528.

Kennedy C, Bajdik CD, Willemze R, et al. The influence of painful sunburns and lifetime sun
exposure on the risk of actinic keratosis, seborrheic warts, melanocytic nevi, atypical
nevi, and skin cancer. *J Invest Dermatol.* 2003;120:1087-1093.

Kwon OS, Bajdik CD, Willemze R, et al. Seborrheic keratosis in the Korean males: causative
role of sunlight. *Photodermatol Photoimmunol Photomed.* 2003;19:73-80.

Tardio JC, et al. Genital seborrheic keratoses are human papillomavirus-related lesions. A lin-
ear array genotyping test study. *APMIS.* 2012;120(6):477-483.

Vun Y, et al. Seborrheic keratosis and malignancy: collision tumour or malignant transforma-
tion? *Australas J Dermatol.* 2006;47:106.

Over 2 million new cases of non-melanoma skin cancer (NMSC) were diagnosed in 2012 in the United States. This number is greater than the annual number of all other newly diagnosed cancers combined. The etiologies of skin cancer include exogenous and endogenous factors that interact to lead to carcinogenesis. Endogenous factors include (i) skin type, (ii) immunosuppression (leukemia, HIV infection, etc.), and (iii) genetic predisposition (family history, basal cell nevus syndrome, xeroderma pigmentosum, etc.). The most important exogenous factor is ultraviolet radiation which promotes immunosuppression, damages chromosomes, and generates reactive oxygen species. Other exogenous factors include (i) ionizing radiation, (ii) chemical carcinogens (arsenic), (iii) human papilloma-virus (HPV), and (iv) chronic irritation (ulcers and burns).

BASAL CELL CARCINOMA

I. BACKGROUND Basal cell carcinomas (BCCs) arise from a pluripotential cell in the basal layer of the epidermis. They make up 75% of all skin cancers.¹ One in every five Americans will develop an NMSC, and 95% of these will be a BCC. They are more common in men and tend to grow very slowly with an extremely low rate of metastasis (0.0028% to 0.55%).² About 80% of BCCs and squamous cell carcinomas (SCCs) occur on the head and neck.¹ Individuals with an NMSC have a 10-fold increased risk for developing a second NMSC, with more than 40% developing a BCC within 3 years.²

II. CLINICAL PRESENTATION

- A. Nodular BCC.** This subtype of BCC has rolled, easily defined borders (Fig. 40-1). The surface has a slightly translucent or pearly quality, often with central crust or ulceration and surface telangiectasias. Nodular BCCs make up 50% to 80% of all BCCs;² 85% to 90% are found on the head and neck.
- B. Superficial BCC.** Superficial BCCs appear as erythematous scaly plaques with irregular, elevated, well-demarcated borders and variable telangiectasias (Fig. 40-2). They are commonly found on the trunk and extremities.²
- C. Sclerosing or Morpheaform BCC.** This type of BCC is a yellow-white, flat or depressed, sclerotic plaque and resembles a scar with indistinct borders (Fig. 40-3). The actual size of the cancer is often greater than can be appreciated by clinical examination.¹

III. WORKUP All suspected skin cancers should be biopsied to confirm the diagnosis and to determine the necessary treatment. Most BCCs can be



Figure 40-1. Nodular basal cell carcinoma. This is a close-up view, showing rolled borders with telangiectasia. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

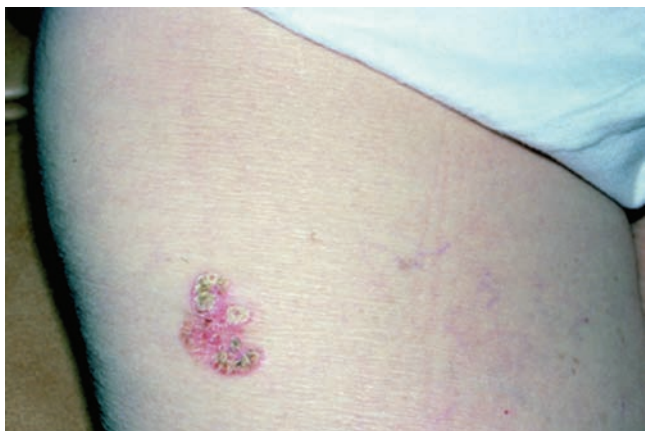


Figure 40-2. Superficial basal cell carcinoma. This lesion resembles a psoriatic plaque as well as Bowen disease. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 40-3. Morpheaform basal cell carcinoma. A whitish atrophic plaque is present, with surrounding telangiectasias and pearly papules surrounding the atrophic plaque. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

biopsied with a tangential shave technique. Larger lesions may require an incisional or excisional biopsy.

IV. TREATMENT The age and health of the patient, size and location of the tumor, and pathology must be considered when planning therapy. Follow-up for NMSC should be on a 6- to 12-month basis.

- A. Standard Excisional Surgery** with 4-mm margins is curative in 98% of non-morpheaform BCCs that are <2 cm in size.¹
- B. Electrodesiccation and Curettage** should be reserved for superficial tumors on non-facial areas. In this technique, the tumor is removed by curettage, and the site is then electrodesiccated with a 1- to 2-mm margin of normal skin. This process is then repeated for a total of three times. Cure rates approach 87% in experienced hands.
- C. Cryotherapy** by spray technique is also inferior to standard excision and should also be reserved for smaller superficial lesions. After injecting local anesthesia, two cycles of a 30-second full freeze with a thaw time of at least 90 seconds should be performed. The site will swell, become painful, and blister over 1 to 2 days. Permanent hypopigmentation is a common side effect.
- D. Mohs Micrographic Surgery** is an excisional surgical technique in which 100% of the margins are examined to determine whether residual tumor is present at the time of surgery. This tissue-sparing technique provides the highest possible cure rate for contiguous tumors such as BCCs and SCCs. Indications for Mohs surgery are sites requiring tissue preservation, high-risk locations, immunosuppression, aggressive pathology, tumors >2 cm, recurrent tumors, and poorly defined tumors. Cure rates for primary BCC are 98% to 99%.¹

- E. 5-Fluorouracil** is a topical therapy for superficial, small BCCs. It is applied twice a day for 4 to 6 weeks. For nodular BCCs, topical treatment is effective only 65% of the time.²
- F. Topical Imiquimod** 5% cream is an immune response modifier that is indicated for the treatment of primary superficial BCCs that are less than 2 cm in diameter on low-risk areas. It is applied 5 times per week for at least 6 weeks with an 80% cure rate for superficial BCCs.²
- G. Ionizing Radiation** is usually reserved for individuals who are poor surgical candidates.
- H. Vismodegib**, an orally bioavailable inhibitor of Hedgehog signaling, was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of locally advanced or metastatic BCCs that are inoperable.³

SQUAMOUS CELL CARCINOMA

- I. BACKGROUND** SCCs arise from epidermal keratinocytes, usually in the setting of moderate-to-severe actinic damage. SCCs make up 25% of all skin cancers.¹ In dark-skinned patients, SCCs are 20% more common than BCCs.² They tend to grow more rapidly than BCCs and may extend along nerves with a metastatic potential of 0.5% to 5.2%.² Lesions on the ear, lip, penis, and dorsum of the hand have a higher metastatic rate; for instance, SCCs on the lower lip metastasize 10% to 15% of the time. In solid organ transplant patients, there is a 65-fold increase in the incidence of SCC.⁴ SCCs behave more aggressively in this group and have a higher rate of metastasis.
- II. CLINICAL PRESENTATION** An SCC typically presents as an enlarging, scaling, dome-shaped nodule that often arises from an actinic keratosis (AK). An AK is a rough scaly papule that develops on sun-exposed areas. The rate of each AK developing into an SCC is 0.075% to 0.096% per lesion per year.¹ Some variants of SCCs are discussed below.
 - A. SCC In Situ** aka Bowen disease appears as a well-demarcated, scaling plaque (Fig. 40-4).
 - B. Bowenoid Papulosis** appears as multiple slightly verrucous papules on the genitalia. They are induced by HPV type 16 or 18 and, while considered premalignant, they are often indolent.¹
 - C. Erythroplasia of Queyrat** is Bowen disease on the glans penis and typically presents as a well-demarcated red plaque.
 - D. A Keratoacanthoma** is a rapidly growing, well-demarcated nodule with a cup-shaped center filled with keratinous material (Fig. 40-5). A classic keratoacanthoma is self-healing over weeks to months, but may show aggressive growth features similar to an invasive SCC. Since differentiation from SCC can be difficult, it is generally treated as an SCC.¹
- III. WORKUP** All suspected skin cancers should be biopsied to confirm the diagnosis and to determine the necessary treatment. A full body skin examination with particular attention to the surrounding skin and lymph nodes should also be undertaken. These growths are easily biopsied by the shave technique.



Figure 40-4. Squamous cell carcinoma. Squamous cell carcinoma usually appears on sun-exposed skin of fair-skinned adults over 60. It may develop in an actinic keratosis. It usually grows more quickly than a basal cell carcinoma, is firm, and looks redder. The face and the back of the hand are often affected, as shown here. (From Westwood Pharmaceuticals. From Hall JC. *Sauer's Manual of Skin Diseases*. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2000.)



Figure 40-5. Keratoacanthoma. This nodule arose over a period of 2 weeks. Note the typical crusting in the center. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

IV. TREATMENT SCCs may be treated with wide local excision with 5-mm margins or Mohs micrographic surgery. Electrodesiccation and curettage, cryotherapy, and topical treatments are not optimal treatments since SCCs are more aggressive than the average BCC. If there is perineural invasion or there is regional lymphadenopathy, the regional lymph nodes should be evaluated for evidence of metastases and additional radiation therapy should be considered after excision. For patients on chronic immunosuppressive medications, an oral retinoid may prevent the development of SCCs.²

MELANOMA

I. BACKGROUND Melanoma is the most common cancer in women aged 25 to 29, and the second most common cancer in women aged 30 to 35. There has been an astounding 15-fold increase in the annual incidence of melanoma over the last 40 years, with an estimated incidence of 59,000 and a mortality rate of 7,700 in the United States in 2005.⁵ Melanoma may arise de novo or in a preexisting nevus. Fair skin, sun exposure, a prior history of psoralen plus ultraviolet A (PUVA) therapy, severe sunburns before the age of 15, family or personal history of melanoma, the presence of dysplastic nevi, and immunosuppression increase the risk of melanoma (Table 40-1, Figs. 40-6, 40.7, and 40-8). A prior personal history of melanoma increases the risk of a second melanoma to 3.4%.⁵ Survival is directly related to early detection.

II. CLINICAL PRESENTATION Itching, bleeding, and rapid change/growth in a mole should arouse suspicion of malignant changes. Melanoma can be found on any surface of the skin. The various types are discussed below.

TABLE 40-1 Factors Associated with Increased Risk of Melanoma	
Factor	Relative Risk (%) ^a
Changing or persistently changed mole, age >15 y	Very high
One or several irregularly pigmented lesions	88
Atypical (dysplastic) mole(s) or familial melanoma (see Fig. 40.6)	148
Atypical (dysplastic) mole(s) but no familial melanoma (see Fig. 40.7)	17–64
Lentigo maligna (see Fig. 40.8)	10
Congenital mole	17–21
White race (compared with blacks)	12
Previous melanoma	5–9
Melanoma in parents, children, or siblings	2–8
Immunosuppression—leukemia, lymphoma, renal transplantation	2–3

TABLE 40-1 (Continued)

Sun sensitivity, tans poorly, burns easily, had multiple or severe sunburns	2–3
Excessive sun exposure, particularly during childhood	3–5
No increased risk	1

^aDegree of increased risk for persons with the risk factor compared with persons without the risk factor. Relative risk of 1.0 implies no increased risk.

(Data from: Rhodes AR, Weinstock MA, Fitzpatrick TB, et al. Risk factors for cutaneous melanoma. A practical method of recognizing predisposed individuals. *JAMA*. 1987;258:3146-3154.)



Figure 40-6. Dysplastic nevus.

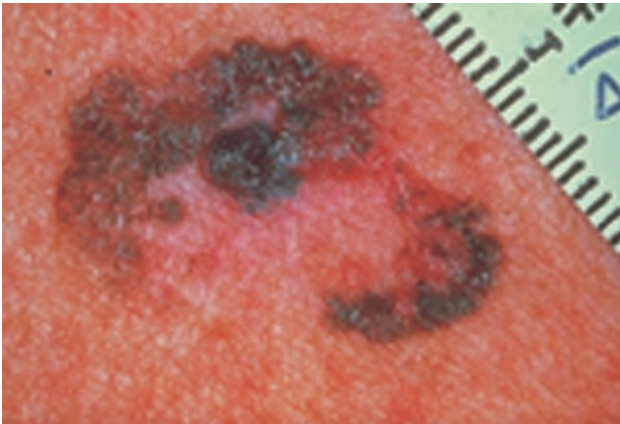


Figure 40-7. Superficial spreading melanoma.



Figure 40-8. Lentigo maligna melanoma.

- A. Superficial Spreading Melanoma.** This lesion appears as a flat to slightly raised pigmented papule or plaque (Fig. 40-9), most commonly found on the back in men and the lower legs in women.⁶ Seventy percent of all melanomas present with this growth pattern.⁵ Features concerning for melanoma are asymmetry, border irregularity, color variegation, diameter greater than 6 mm, and recent changes/growth.
- B. Lentigo Maligna Melanoma (LMM).** LMM occurs on sun-exposed areas, especially on the face of elderly patients, and makes up 14% of all melanomas.⁵ LMM starts as lentigo maligna, aka Hutchinson freckle (Fig. 40-10), an irregularly pigmented macule with a jagged border. Five percent of lentigo malignas transform to LMM.⁵ The onset of nodular growth is slow and usually occurs 5 to 20 years after the development of the precursor lentigo maligna.⁶
- C. Nodular Melanoma.** This tumor is characterized by rapid vertical growth without a significant radial growth phase.⁶ The pigment may be brown, black, or blue (Fig. 40-11); however, amelanotic melanoma lesions appear as nonspecific red papules that mimic BCCs or cysts. This variant makes up 15% to 30% of all melanomas.⁵
- D. Acral Lentiginous Melanoma.** This form of melanoma occurs on palms, soles, fingers, and toes and is the most common form of melanoma in blacks and Asians.⁶ A pigmented streak in a nail warrants suspicion; pigmentation of the cuticle adjacent to the nail is suggestive of involvement of

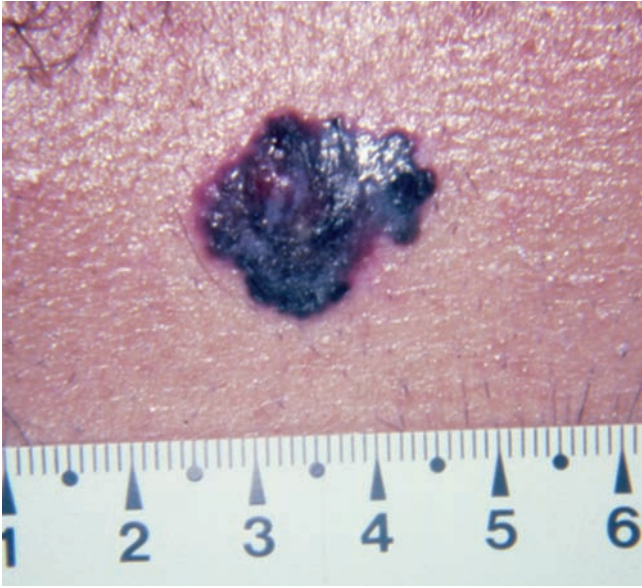


Figure 40-9. Superficial spreading melanoma. Note the “ABCD” features: asymmetry, notched border, varied colors, and diameter of more than 6 mm. (From Goodheart HP. *Goodheart’s Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 40-10. Lentigo maligna. Note the irregular color and irregular border of this malignant melanoma in situ. (From Goodheart HP. *Goodheart’s Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 40-11. Nodular melanoma. This is a nodule with surrounding satellite lesions that represent local “in-transit” metastases. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

the nail matrix (Hutchinson sign) (Fig. 40-12). This subtype accounts for 5% to 10% of all melanomas.⁵

III. WORKUP

A. A Shave Biopsy should only be done if it is deep enough that no pigment is left at the base; for this reason, a punch or excisional biopsy may be preferable. Larger lesions, such as an LMM, can be biopsied in the most darkly pigmented, nodular area by an incisional or punch biopsy, or a broad superficial shave of the entire lesion can be done.⁶ Melanoma staging is based on the tumor node metastasis (TNM) system which uses tumor size, nodal, and metastatic status (Table 40-2). The T classification incorporates Breslow thickness, ulceration, and mitotic rate. Breslow thickness is the distance from the granular layer to the deepest tumor cell measured in millimeters.

1. TNM Classification Tis: in situ melanoma

T1: ≤ 1 mm Breslow thickness

T1a: Without ulceration and mitosis $< 1/\text{mm}^2$

T1b: With ulceration or mitoses $\geq 1/\text{mm}^2$

T2: 1.01 to 2.0 mm

T2a: Without ulceration

T2b: With ulceration

T3: 2.01 to 4.0 mm

T3a: Without ulceration

T3b: With ulceration



Figure 40-12. Acral lentiginous melanoma. Hutchinson sign shows uneven pigmentation spreading beyond the nail into surrounding skin. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

TABLE 40-2 2009 American Joint Committee on Cancer Stage Groupings for Cutaneous Melanoma			
Stage	Primary Tumor (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
Clinical Staging			
O	Tis	NO	MO
IA	T1a	NO	MO
IB	T1b	NO	MO
	T2a	NO	MO
IIA	T2b	NO	MO
	T3a	NO	MO
IIB	T3b	NO	MO
	T4a	NO	MO
IIC	T4b	NO	MO
III	Any T	N1, N2, or N3	MO
IV	Any T	Any N	M1

(Continued)

TABLE 40-2	2009 American Joint Committee on Cancer Stage Groupings for Cutaneous Melanoma (Continued)		
Pathologic Staging			
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-4a	N1a	M0
	T1-4a	N2a	
	T1-4b	N1a	
IIIB	T1-4b	N1a	M0
	T1-4b	N2a	
	T1-4a	N1b	
	T1-4a	N2b	
	T1-4a	N2c	
IIIC	T1-4b	N1b	M0
	T1-4b	N2b	
	T1-4b	N2c	
	Any T	N3	
IV	Any T	Any N	Any M

(Adapted from Balch M, Gershenwald J, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol.* 2009;27:6199-6206.)

- T4: >4 mm
- T4a: Without ulceration
- T4b: With ulceration
- The parameters for N classification
 - N0: No regional node metastasis
 - N1: Metastasis in one regional node
 - N1a: Micrometastasis
 - N1b: Macrometastasis
 - N2: Metastasis in two to three regional nodes
 - N2a: Micrometastasis
 - N2b: Macrometastasis
 - N2c: In-transit or satellite metastasis without nodal metastasis

N3: Metastasis in greater than or equal to four regional nodes, matted nodes, or in-transit or satellite metastasis with positive metastatic nodes.

M0: No distant metastasis

M1: Distant metastases

M1a: Distant skin, subcutaneous, or lymph node metastasis

M1b: Lung metastasis

M1c: All other visceral metastases with normal lactate dehydrogenase (LDH) or any distant metastasis with elevated LDH.

B. Sentinel Lymph Node Biopsy (SLNB) is a sensitive detection technique to find occult metastatic lymph node foci without performing a total lymph node dissection. Detection of a positive sentinel lymph node is predictive of regional node metastases and is an indication for elective lymph node dissection and/or adjuvant therapy. The American Joint Committee on Cancer (AJCC) now recommends SLNB for patients with T1b, T2, T3, and T4 melanoma.

C. A Baseline Chest X-Ray and Baseline and Serial LDH should be checked in stage Ib and above.⁶ Serum LDH is a predictor of survival in patients with stage IV disease. The most common sites of distant metastases are skin, lymph nodes, lung, liver, brain, and bone. Imaging such as computed tomography, magnetic resonance imaging, and positron emission tomography scans are indicated in advanced melanoma.

IV. TREATMENT

A. Wide Local Excision is the standard treatment for primary melanoma and should be done within 3 weeks of diagnosis.⁵ The following is a guideline for lateral excisional margins:

- Melanoma in situ: At least 0.5-cm margin
- <1-mm deep: 1-cm margin
- 1 to 2 mm in depth: 1- to 2-cm margin
- >2 mm in depth: ≥ 2 cm

B. Regular Follow-Up is crucial. A full body skin examination, including the scalp, oral mucosa, and genitalia, is recommended by the American Academy of Dermatology every 3 months for the first 2 years and then every 6 to 12 months thereafter.⁵

C. Treatment of Metastatic Disease may include **chemotherapy and radiation**, but the overall results in metastatic disease are disappointing. Patients with non-regional lymph node metastases and gastrointestinal metastases have a median survival rate of 12.5 months, while liver, bone, or brain metastases have a median survival of 4.4 months.⁵

D. Interferon α -2b is FDA approved as an adjuvant treatment.⁶ Though it may prolong relapse-free survival, its impact on overall survival is doubtful.

E. Vemurafenib, an inhibitor of mutated BRAF, has proven useful for prolonging progression-free and overall survival in patients with previously untreated melanoma with the BRAF V600E mutation.⁷

F. In 2011, the FDA Approved Ipilimumab, an anti-CTLA4 antibody, for the treatment of metastatic melanoma.

G. In 2013, the FDA Approved Two Drugs, dabrafenib and trametinib, for the treatment of advanced (metastatic) or unresectable melanoma.

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REFERENCES

1. Bolognia JL, Jorizzo JL, Rapini RP. Actinic keratosis, basal cell carcinoma and squamous cell carcinoma. In: *Dermatology*. 2nd ed. Philadelphia, PA: Elsevier; 2008:1641-1658.
2. James W, Berger T, Elston D. Epidermal nevi, neoplasms, and cysts. In: *Andrews' Diseases of the Skin*. 11th ed. Philadelphia, PA: Elsevier; 2011:633-644.
3. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med*. 2012;366(23):2171-2179.
4. Bangash HK, Colegio OR. Management of non-melanoma skin cancer in immunocompromised solid organ transplant recipients. *Curr Treat Options Oncol*. 2012;13 (3):354-376.
5. Bolognia JL, Jorizzo JL, Rapini RP. Melanoma. In: *Dermatology*. 2nd ed. Philadelphia, PA: Elsevier; 2008:1745-1766.
6. James W, Berger T, Elston D. Melanocytic nevi and neoplasms. In: *Andrews' Diseases of the Skin*. 11th ed. Philadelphia, PA: Elsevier; 2011:685-690.
7. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364:2507-2516.

- I. BACKGROUND** Skin tags, also known as acrochordons, are very common soft, fleshy, skin-colored round to oval pedunculated papules with predilection for the neck, axillae, trunk, groin, and eyelids of middle-aged and elderly people. Skin tags are benign, and predisposing factors include obesity, pregnancy, menopause, and acromegaly. In the past, there was thought to be an association with colonic polyps, but more recently this relationship has been disputed.
- II. CLINICAL PRESENTATION** Patients are usually bothered by the cosmetic appearance of skin tags. They are usually asymptomatic, but can be irritating when repeatedly caught on clothing and painful when a lesion twists on its own stalk and infarcts. The lesions are single or multiple, 1 to 10 mm in diameter, soft, flesh-colored or hyperpigmented, oval or round pedunculated fleshy papules, and tend to increase in size over time.
- III. WORKUP** Lesions may be confused with other benign neoplasms such as seborrheic keratoses, intradermal nevi, neurofibromas, and warts. Malignant neoplasms mistaken for skin tags include amelanotic melanoma and fibroepithelioma of Pinkus. Skin tags have been implicated as a marker for diabetes; however, this relationship remains controversial. Colonoscopy is no longer recommended with the appearance of multiple skin tags.
- IV. TREATMENT** Treatment is easily accomplished with any of the following methods:
- A. Excision by Scissor Snip.** Grasp the skin tag with forceps and snip the base with a sharp scissors. Hemostasis may be achieved by pressure or 20% aluminum chloride. Local anesthesia with lidocaine is optional.
 - B. Destruction by Electrofulguration.** Grasp the skin tag with forceps and remove each lesion with the cutting current. Local anesthesia with lidocaine is optional and may cause as much pain as the treatment itself.
 - C. Cryotherapy.** Grasp the base of the skin tag with a forceps and direct liquid nitrogen spray at the lesion until frozen. The use of the forceps helps prevent transmission of the liquid nitrogen to the non-lesional skin. Alternatively, dip the tip of a hemostat, forceps, or needle holder into liquid nitrogen for 15 seconds without allowing the hinge to freeze. Use this instrument to grasp the lesion for 10 seconds. A cotton-tipped applicator dipped in liquid nitrogen can also be used to freeze the lesion, although this can lead to damage to the surrounding tissue.

Suggested Readings

- Akhtar AJ, Zhuo J. Non-association between acrochordons and colonic polyps in a minority population. *J Natl Med Assoc.* 2003;95(8):746-749.
- Amster MS, Klaus MV. Amelanotic melanoma. *Arch Dermatol.* 1995;131(8):953-954.
- Choudhary ST. Treatment of unusually large acrochordon by shave excision and electrodesiccation. *J Cutan Aesthet Surg.* 2008;1(1):21-22.
- El Safoury OS, Ibrahim M. A clinical evaluation of skin tags in relation to obesity, type 2 diabetes mellitus, age and sex. *Indian J Dermatol.* 2011;56(4):393-397.
- Goodheart HP. Surgical pearl: a rapid technique for destroying small skin tags and filiform warts. *Dermatol Online J.* 2003;9:34.
- Su MW, Fromer E, Fung M. Fibroepithelioma of Pinkus. *Dermatol Online J.* 2006;12(5):2.

I. BACKGROUND The sun's emission spectrum is extremely broad, whereas the spectrum that reaches earth is limited to the wavelengths of ultraviolet radiation (UVR), visible light, and infrared radiation. UVR can be further subdivided into three categories:

1. UVA (A-I 340 to 400 nm, A-II 320 to 340 nm) constitutes over 90% of the UVR that reaches earth and penetrates deeply to the dermis contributing to immediate and long-term cutaneous damage by degenerating collagen.¹ UVA may induce severe phototoxicity in combination with some medications such as psoralens, doxycycline, sulfonamides, phenothiazines, and sulfonyleureas.
2. UVB (290 to 320 nm) is the primary cause of cutaneous erythema and edema. Chronic exposure to UVB leads to aging and carcinogenesis.
3. UVC (200 to 290 nm) wavelengths are blocked by the ozone layer and do not reach earth's surface. They can also be found in commercial germicidal lamps and can cause mild conjunctivitis or sunburn.

Sunburn is an acute inflammatory reaction of the skin that results from overexposure to UVR. Upon exposure to UVR, cutaneous blood vessels in the upper dermis vasodilate, resulting in a subsequent increase in vascular permeability, edema, and erythema. Mast cells then release mediators such as histamine, serotonin, and tumor necrosis factor, which stimulate prostaglandin and leukotriene production. Cytokines are released, further stimulating inflammation and an increase in neutrophil and T-cell migration. This cascade results in the production of reactive oxygen species which damage DNA leading to the formation of pyrimidine dimers and subsequent mutations.¹ This can result in the inactivation of tumor suppressor genes, e.g., p53, which has been shown to eventuate in the development of non-melanoma skin cancers.² UVR exposure has also been shown to suppress cutaneous cell-mediated immunity with altered response to antigens, release of immunosuppressive factors such as interleukins, and inhibition of natural killer cells, resulting in an increased risk for the development of non-melanoma skin cancers and infectious disease. Finally, a number of diseases known as photodermatoses may be caused or exacerbated by UVR exposure (Table 42-1).

UVR exposure leads to an increase in skin pigmentation, or suntan, which offers some protection against further sun exposure. This process occurs in two ways:

1. Immediate pigment darkening (IPD) begins 2 to 24 hours after exposure to UVA, which causes metabolic alterations and redistribution of existing melanin. IPD is not photoprotective.
2. Delayed pigment darkening begins 2 to 3 days after exposure to UVB, which causes DNA damage and gene alterations leading to the synthesis of melanin.³ This increase in pigment typically lasts a few weeks and offers some natural protection from further UVR exposure. However, because

TABLE 42-1	Photodermatoses
Genetic: xeroderma pigmentosum	
Metabolic: pellagra, porphyria cutanea tarda	
Neoplastic: actinic keratosis, basal cell carcinoma, squamous cell carcinoma, melanoma	
Connective tissue: systemic lupus erythematosus	
Immunologic: solar urticarial, drug photoallergy	
Idiopathic: solar urticarial, actinic prurigo, polymorphous light eruption, chronic actinic dermatitis	

it is associated with underlying damage, tanning is not recommended for photoprotection.

A variety of factors influence the likelihood of developing a sunburn. Natural sun-protective mechanisms include thickness of the epidermis, natural antioxidants, melanin, urocanic acid (natural UV absorber), DNA repair mechanisms, and Fas ligand signaling.¹ Tolerance to sunlight is based on the amount of melanin in the skin and an individual's genetic capacity to produce melanin, or tan, following exposure to UVR. Hydrated skin absorbs a larger percentage of UVR and is therefore more easily damaged. Additionally, a significant proportion of UVR reaches the skin through reflection from snow, sand, or sidewalks. Exposure to UVR is greatest from 10 am to 4 pm and increases at higher altitudes and latitudes closer to the equator.

Fitzpatrick developed a classification system for the response of different skin types to UVR (Table 42-2). The minimal dose of UVR necessary to produce erythema of an unprotected site is known as the minimal erythema dose (MED). This dose varies based on skin type which is categorized on the basis of the sun-reaction response to the first 30-minute exposure to summer sun. People with type I and II skin will exceed their sunburn threshold tolerance

TABLE 42-2	Fitzpatrick Skin Types and Response to First 30-Minute Exposure to Summer Sun
Skin Type	Response
I	Always burns easily, never tans
II	Usually burns easily, tans minimally
III	Burns moderately, tans gradually
IV	Burns minimally, tans readily
V	Rarely burns, tans profusely, and occurs in heavily pigmented individuals
VI	Never burns, darkly pigments, and occurs in blacks

in 10 to 20 minutes of noontime temperate summer sunlight. Three to eight times the MED will produce a moderate-to-severe burn.

The diminishing ozone layer has been a concern over the past 40 years. Regulations to limit production of ozone-depleting materials have slowed its destruction, but there has been no regeneration. As a consequence, more UVB can now reach earth's surface. The impact of climate changes caused by the stratospheric ozone depletion on skin cancer incidence remains uncertain. To help people better understand the intensity of UV light in their area, the Environmental Protection Agency and the National Weather Service developed the UV Index (Table 42-3), a program that informs the public about the amount of harmful UVR reaching the earth on a particular day. The National Meteorological Center determines the index daily, and it is a recognized part of the weather report in many cities.

II. CLINICAL PRESENTATION Patients with sunburns most often report a history of recent sun exposure, outdoor activity or indoor tanning. High-risk patients include those with Fitzpatrick skin types I and II. Characteristic diffuse, continuous erythema typically develops approximately 3 to 6 hours after exposure to UVB, and patients may have pain and sensitivity over the area. Symptoms usually peak in 16 to 24 hours. Severe burns are accompanied by intense pain, inability to tolerate contact with clothing and sheets, as well as constitutional signs and symptoms, including nausea, tachycardia, chills, hypotension, and fever. In patients with severe burns, it is important to evaluate for exposure to photosensitizing drugs and the presence of underlying factors such as topical application of photosensitizers or systemic illnesses such as lupus or porphyria (Fig. 42-1).

The earliest sign of a burn is a pink to scarlet hue of the skin and mild edema. The more severe the burn, the earlier these changes will be evident. Overexposure to the sun causes immediate erythema which then fades. A delayed erythema appears in 2 to 4 hours, peaks at 14 to 20 hours, and lasts 24 to 72 hours.² Severe burns may progress to a vivid erythema, intense edema, and blistering (Fig. 42-2). Desquamation follows as a consequence of increased

TABLE 42-3 Ultraviolet Index and Recommendations from the National Meteorological Center	
UV Index	Recommendation
0–2: Minimal	One hour of unprotected exposure may produce UV damage in people with sun-sensitive skin
3–4: Low	Sunburn may occur within 30–60 min of unprotected exposure
5–6: Moderate	Significant risk of skin damage and sunburn in only 20–30 min of unprotected exposure
7–9: High	Unprotected skin may burn in 10–20 min
10–15: Very high	Burning will occur in <10 min without protection



Figure 42-1. Patient with sunburn causing a psoriasis exacerbation secondary to the Koebner phenomenon. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 42-2. Severe sunburn with bullae formation. (From Fleisher GR, Ludwig S, Baskin MN. *Atlas of Pediatric Emergency Medicine*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

epidermal turnover during the repair response, usually a week or more after the burn.

III. PREVENTION Prevention is the best approach and consists of avoiding sun exposure during peak hours, proper application of sunscreens, and wearing protective clothing. Clothing is rated by its ability to block UVB radiation, referred to as ultraviolet protection factor (UPF), but it is possible to obtain a sunburn through clothing. The amount of UPF provided by clothing varies by the material, weave, color, and fit as well as whether the article of clothing is wet or dry.

Sun-protective topical medications are available as sunscreens, which contain multiple chemical substances and physical blockers. Organic (chemical) sunscreens contain compounds that absorb UV rays and are excited to a higher energy state, which then dissipates as heat or emission at longer wavelengths.¹ Their primary ingredients typically include *para*-aminobenzoic acid (PABA), PABA esters, salicylates, and benzophenones. The inorganic (physical) sunscreens contain small particles such as zinc oxide, titanium dioxide, iron oxide, and kaolin which scatter and reflect UV radiation. Most sunscreens have peak absorption rates in the range of UVB; however, the level of UVA protection has been the subject of recent studies and recommendations by the U.S. Food and Drug Administration (FDA).

The sun protection factor (SPF) value is defined as the dose of UVR required to produce one MED on protected skin after the application of 2 mg/cm² of product divided by that of unprotected skin. The SPF usually ranges from 2 to 100 with 50% protection from SPF 2, 93% protection from SPF 15, and 97% protection from SPF 34. The FDA recently recommended that SPF be changed to sunburn protection factor, as it measures the protection against erythema, a function of UVB. Many people have the misconception that application of sunscreen will offer complete protection against sun-induced skin damage, and the use of higher SPF sunscreens appears to give users a false sense of security, resulting in an increase in the duration of recreational sun exposure.

Although the general public is starting to wear sunscreen on a daily basis, studies have shown that it is not being used correctly. The average person applies only one-quarter to one-half of the recommended amount of sunscreen, and at half of the recommended amount, the SPF can be reduced by as much as a power of 2. The use of a higher SPF can partially compensate for under-application.⁴ For a sunscreen to be effective, a layer of 0.5 mm should be applied or approximately a quarter of most standard-sized bottles of sunscreen when applied to the entire body. Reapplication every 60 to 90 minutes is necessary to maintain effectiveness, depending on the formulation and the activity level of the person. The American Academy of Dermatology recommends application of a broad-spectrum, water-resistant sunscreen with an SPF of at least 30 to be worn year round regardless of skin type (Table 42-4).

In June 2011, the FDA developed new regulations and recommendations regarding the prevention and treatment of sunburn. These took effect in June 2012, resulting in a change in the requirements for broad-spectrum designation; any product now claiming this title is required to comply with standardized testing to prove protection against both UVA and UVB. Any sunscreen

TABLE 42-4 Guidelines for Sunscreen Use

- a. Select a sunscreen with SPF 30 or above that has both UVA and UVB protection
- b. Apply sunscreen 15–30 min before exposure; reapply 30 min after sun exposure and every 2 h or after swimming, exercising, or toweling
- c. Select a water-resistant sunscreen for beach or outdoor activities associated with perspiring
- d. Wear dark, loose, dry long-sleeved clothing with a tight weave and a wide-brim hat
- e. Avoid peak sunlight hours (10 am to 4 pm)
- f. Children <6 mo of age should have sunscreen applied to the exposed areas; titanium dioxide–containing sunscreens are safe and are less likely to irritate the skin. Sun-protective clothing and avoidance are strongly recommended in this age group
- g. For maximum eye protection, pick wraparound sunglasses that fit close to the forehead and absorb up to 400 nm in the UVA, UVB, and blue light range

SPF, sunburn protection factor; UVA, ultraviolet A; UVB, ultraviolet B.

that is not broad spectrum or has an SPF value between 2 and 13 will have a warning label that reads, “Skin Cancer/Skin Aging Alert: Spending time in the sun increases your risk of skin cancer and early skin aging. This product has been shown only to help prevent sunburn, not skin cancer or early skin aging.” Recommendations also included labeling any sunscreen greater than an SPF of 50 with an “SPF 50+s.” The descriptors “waterproof” and “sweat proof” are no longer allowed, and the label will state that a product is water resistant for up to 40 or 80 minutes.

Sunscreen has been shown to prevent ultraviolet-induced DNA damage, cutaneous immunosuppression, and the generation of T suppressor cells. Additionally, application of sunscreens does decrease the risk for the development of non-melanoma skin cancers and actinic keratoses; its effect on the prevention or development of melanoma is controversial.⁴ Chronic use of sunscreen does alter vitamin D synthesis; a normal diet should compensate for this. Patients whose diet may be low in vitamin D should be tested and given supplements as needed.

The use of indoor tanning beds is a lucrative industry in the United States, but many dermatologists, pediatricians, and others are voicing concerns due to the lack of regulation. Sunlamps, which use primarily UVA wavelengths, emit as much as 26 times more damaging UV exposure than the equivalent increment of sunlight. While this can produce erythema and melanogenesis, it does not provide the protection of a naturally acquired tan. The carcinogenic effect of exposure to these sunlamps is a major concern with studies showing a significant increase in the risk of cutaneous melanoma and non-melanoma skin cancers. One study demonstrated a 55% increased risk for melanoma following accumulation of 40 hours of sun bed use.¹

TABLE 42-5	Primary Treatment Options
<ol style="list-style-type: none">1. Prevention2. Cool compresses and soaks3. Emollients4. Pain control with nonsteroidal anti-inflammatory drugs or acetaminophen5. Topical and systemic corticosteroids	

IV. TREATMENT Uncomplicated sunburn is a self-limited process with excellent prognosis. Most cases resolve without significant sequelae. Unfortunately, severe and diffuse sunburns may lead to second-degree burns with blister formation, dehydration, and the potential for secondary infections.

Treatment of minor sunburn consists of symptomatic relief with cool compresses, emollients, and pain control. Regardless of the treatment modality, the UV damage to epidermal cells remains unchanged. Because burns are intrinsically self-healing, it is mandatory that the therapy be less noxious than the problem (Table 42-5).

- A. Cool Compresses and Soaks in Water or Burrow Solution.** The symptoms of a minor sunburn may be partially relieved by cool compresses or baths.
- B. Nonsteroidal Anti-inflammatory Drugs (NSAIDs).** Topical and systemic NSAIDs cause an early and mild reduction of erythema due to anti-inflammatory and antiprostaglandin effects but only if taken immediately before or after sun exposure.² This is problematic as most patients seek treatment only after symptoms have developed. NSAIDs and other over-the-counter analgesics may be beneficial in terms of pain relief.
- C. Topical or Systemic Corticosteroids.** Little evidence exists to support claims that topical or systemic corticosteroids shorten recovery times significantly though use is frequently described in the literature. If used, oral steroids should be prescribed for only a few days and do not require a taper.² Corticosteroids are best avoided in second-degree burns as they may increase the risk of infection.
- D. Topical Anesthetics.** While topical anesthetics may be effective for pain relief, preparations containing benzocaine, a sensitizer, should be avoided.
- E. Emollients.** Studies of various emollients have failed to demonstrate improved recovery times; however, many patients find that emollients such as aloe vera provide temporary relief of sunburn symptoms. This is most likely secondary to an improvement in cutaneous hydration as well as evaporative cooling.
- F. Fluid Replacement.** Severe burns require fluid replacement (oral or intravenous) to avoid or correct dehydration.
- G. Gentle Skin Care and Sun Avoidance.** Following a sunburn, patients should avoid the sun as much as possible. For patients with blistering sunburns, the blister roofs should be left intact if possible. If the roof is

extremely flaccid or on an area of high mobility or friction, the blister may be unroofed so that the skin can be bandaged appropriately.

H. Topical or Systemic Antibiotics. If a patient develops a secondary infection, antibiotics may be necessary.

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REFERENCES

1. Volkovova K, Bilanicova D, Bartonova A, Letašiová S, Dusinska M. Associations between environmental factors and incidence of cutaneous melanoma. Review. *Environ Health*. 2012;11(Suppl 1):S12.
2. Han A, Maibach HI. Management of acute sunburn. *Am J Clin Dermatol*. 2004;5(1):39-47.
3. Moyal D. Need for a well-balanced sunscreen to protect human skin from both ultraviolet A and ultraviolet B damage. *Indian J Dermatol Venereol Leprol*. 2012;78:24-30.
4. Ou-Yang H, Stanfield J, Cole C, Appa Y, Rigel D. High-SPF sunscreens may provide ultraviolet protection above minimal recommended levels by adequately compensating for lower sunscreen user application amounts. *J Am Acad Dermatol*. 2012;67(6):1220-1227.

Suggested Readings

- Danno, K, Horio, T. Sunburn cell: factors involved in its formation. *Photochem Photobiol*. 1987;45(5):683-690.
- Lehmann, P, Schwarz, T. Photodermatoses: diagnosis and treatment. *Dtsch Arztebl Int*. 2011;108(9):135-141. [Epub 2011 Mar 4].
- Walker SL, Hawk JL, Young AR. Acute effects of ultraviolet radiation on the skin. In: Freedberg IM, ed. *Fitzpatrick's Dermatology in General Medicine*. 6th ed. New York, NY: McGraw-Hill; 2003:1275-1282.

I. BACKGROUND Telangiectasias are small dilated superficial blood vessels that are blanchable with pressure. These lesions are more common in fair-skinned individuals with chronic sun exposure and rosacea. **Spider telangiectasia (nevus araneus)** is seen most commonly on the face and upper trunk in women and children. These are small telangiectasias radiating from a central arteriole. Acquired lesions may appear in relation to liver disease, such as hepatitis and cirrhosis, or in relation to changes in estrogen metabolism. The most common cause of acquired facial telangiectasia is chronic ultraviolet rays exposure. Other causes of facial telangiectasia include connective tissue disease, prolonged use of topical corticosteroids, rosacea, and postrhinoplasty “red nose” syndrome.

Telangiectasias can also be a manifestation of systemic diseases. **Osler-Weber-Rendu syndrome** (hereditary hemorrhagic telangiectasia or HHT) is an autosomal dominant disease with clinical manifestations such as matlike telangiectasias on the face, tongue, hands, and feet in the context of recurrent epistaxis or internal gastrointestinal bleeding. **CREST syndrome** (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia) patients often develop hyperpigmentation on sun-exposed areas. **Progressive systemic sclerosis** may present with telangiectasia early in the course of disease. Sclerotic changes initially involve face and extremities, but eventually involve larger areas of the body.

II. CLINICAL PRESENTATION See Figures 43-1 and 43-2. Persistent dilations of small capillaries are visible as bright red lines or net-like patterns on the skin. **Spider telangiectasias** consist of a bright red central popular punctum with radiating branches, resembling a spider. The central arteriole may be pulsating, but the radiating telangiectasia blanches with pressure. Patients with multiple telangiectasias of the face may complain of generalized facial erythema.

If a patient presents with blood in the stool, anemia, and red telangiectasias on his lips and fingers, the most likely cause is **HHT**. Patients suffering from HHT develop mucocutaneous telangiectasias, punctuate telangiectasias of fingers, and/or arteriovenous malformations.

III. WORKUP Diagnosis is typically based on clinical findings. A complete history and physical examination may indicate the need for additional investigation to evaluate the underlying etiology of acquired telangiectasias resulting from systemic disease. Complete blood count, urinalysis, renal function tests, chest radiography, antinuclear antibody test, and further imaging may be warranted to rule out systemic causes for cutaneous telangiectasias (Table 43-1).



Figure 43-1. Telangiectasias on the nose. (Courtesy of Shang I Brian Jiang, MD.)



Figure 43-2. Telangiectasia on the cheek.

TABLE 43-1 Differential Diagnosis

- Telangiectasia
- Spider angioma
- Hereditary hemorrhagic telangiectasia
- Ataxia–telangiectasia
- Progressive systemic sclerosis
- CREST syndrome

CREST, calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia.

IV. TREATMENT Telangiectasias are noninvasive, asymptomatic, and do not require treatment unless they are symptomatic. Facial telangiectasias are often a cosmetic problem.

- A. Lasers.** The 595-nm pulsed-dye laser (PDL) is a very effective instrument for the treatment of widespread, matted ectasias. However, PDL therapy can be complicated by post-therapy purpura caused by rapid heating of the vessels. The newer PDLs are equipped with cooling devices and longer pulse durations, thereby minimizing purpura while maintaining efficacy. For the treatment of smaller, linear vessels, the frequency-doubled Nd:YAG/KTP (532 nm) laser may be preferable given its small spot size and less frequent posttreatment purpura. Lasers with longer wavelengths such as 1,064-nm Nd:YAG may also be useful to target vessels that are larger and deeper. However, these longer wavelength lasers have an increased risk of ulcerating and/or scarring.
- B. Intense Pulsed Light (IPL).** The newer generation of IPLs can be effective not only for pigmented lesions but also for the treatment of telangiectasias, leg veins, or cherry angiomas. Multiple studies confirm effective and safe clearance of telangiectasias using IPL systems. Given its large spot sizes and decreased incidence of purpura, the IPL is a good alternative to the existing laser devices particularly for superficial telangiectases involving larger areas.
- C. Electrosurgery.** Electrosurgery can be used for the treatment of spider ectasias, and electrocoagulation is more effective than electrodesiccation. If local anesthesia is used, mark the “body” of the spider angioma prior to injection.

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Suggested Readings

- Clementoni MT, Gilardino P, Muti GF, et al. Facial telangiectasias: our experience in treatment with IPL. *Lasers Surg Med.* 2005;37(1):9-13.
- Fodor L, Ramon Y, Fodor A, et al. A side-by-side prospective study of intense pulsed light and Nd:YAG laser treatment for vascular lesions. *Ann Plast Surg.* 2006;56(2):164-170.
- Nymann P, Hedelund L, Haedersdal M. Long-pulsed dye laser vs. intense pulse light for the treatment of facial telangiectasias: a randomized controlled trial. *J Eur Acad Dermatol Venereol.* 2010;24(2):143-146.
- Tanghetti EA. Split-face randomized treatment of facial telangiectasia comparing pulsed dye laser and an intense pulsed light handpiece. *Lasers Surg Med.* 2012;44(2):97-102.

I. BACKGROUND Urticaria is a heterogeneous group of conditions that are characterized by a similar skin eruption presenting as the sudden appearance of wheals, pruritus, and/or angioedema (Fig. 44-1). It is estimated that 12% to 22% of people will experience acute urticaria at least once in their lifetime. Classification of the many types of urticaria is based on duration, frequency, and cause. In acute urticaria, wheals and/or angioedema resolve in less than 6 weeks, and most episodes are due to adverse reaction to one of the following:

- Food
- Insect stings
- Acute infection or febrile illness
- Immunologic reaction to blood products
- Adverse effect of medication [most commonly penicillin, opiates, and nonsteroidal anti-inflammatory drugs (NSAIDs)] (Fig. 44-2).

Chronic urticaria, occurring in 0.5% of the general population, is characterized by episodes persisting longer than 6 weeks and is divided into two subgroups: chronic autoimmune urticaria and chronic idiopathic urticaria. A majority of cases of chronic urticaria are idiopathic. It has been associated with chronic parasitic infections (helminthes) and chronic infections in protected sites such as sinus, dental, and gallbladder infections. An association between thyroid autoimmunity and chronic urticaria has also been reported. The physical urticarias comprise a separate group of conditions in which urticaria is induced by an exogenous source. Table 44-1 provides a summary of the types of urticaria.

Histamine derived from mast cells is the primary mediator of urticaria. Histamine release causes vasodilation and increased vessel permeability, thereby leading to erythema and edema, respectively. Histamine release from basophils may play a small role in urticaria. Mast cells may also release non-histamine mediators that promote increased vascular permeability (prostaglandin D2 and leukotriene C4) or upregulate adhesion molecules on endothelial cells leading to increased leukocyte adhesion (tumor necrosis factor- α and interleukin-4).

Cutaneous mast cells release histamine in response to many triggers. An IgE-mediated process is presumed to occur in patients with a history of atopy and in urticaria provoked by food, drugs, and aeroallergens. Mast cells can also be triggered to release histamine directly by substances such as complement 5a, morphine, and codeine. The mechanism of autoimmune urticaria is thought to be due to an IgG antibody to IgE or the IgE receptor on mast cells.

II. CLINICAL PRESENTATION The typical lesions of urticaria are raised, erythematous, edematous, plaques of varying sizes with sharply defined serpiginous or polycyclic borders that involve the superficial portion of the dermis and may occur anywhere on the body. More edematous lesions may present with



Figure 44-1. A typical urticarial lesions (wheal) showing dermal edema with no epidermal change. (With permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 44-2. Urticarial drug eruption showing typical annular, erythematous, edematous plaques of varying sizes. (With permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

TABLE 44-1 Classification of Urticaria

Type	Eliciting Factor	Diagnostic Approach
Acute urticaria	<ul style="list-style-type: none"> • Unknown 	<ul style="list-style-type: none"> • None
Chronic urticaria	<ul style="list-style-type: none"> • Unknown 	<ul style="list-style-type: none"> • Blood work—complete blood count with differential, erythrocyte sedimentation rate, thyroid hormone, thyroid autoantibodies • Omission of offending drugs • Test for infectious disease (<i>Helicobacter pylori</i>) • Allergen-free diet • Consider skin biopsy
Cold contact urticaria	<ul style="list-style-type: none"> • Cold objects, air, fluid, wind • Lesions appear as skin begins to warm 	<ul style="list-style-type: none"> • Cold provocation and threshold test with an object such as water or an ice cube at 0–4°C.
Delayed pressure urticaria	<ul style="list-style-type: none"> • Vertical pressure • Wheals arise with a 3–12 h latency 	<ul style="list-style-type: none"> • Pressure test (0.2–1.5 kg/cm² for 10–20 min)
Heat contact urticaria	<ul style="list-style-type: none"> • Localized heat 	<ul style="list-style-type: none"> • Heat provocation and threshold test
Solar urticaria	<ul style="list-style-type: none"> • UV and/or visible light 	<ul style="list-style-type: none"> • Exposure to UV and visible light of different wavelengths
Dermatographic urticaria/urticaria factitia	<ul style="list-style-type: none"> • Mechanical shearing forces such as stroking or scratching 	<ul style="list-style-type: none"> • Elicit dermatographism
Vibratory urticaria	<ul style="list-style-type: none"> • Vibratory forces 	<ul style="list-style-type: none"> • None

(Continued)

TABLE 44-1 Classification of Urticaria (Continued)		
Type	Eliciting Factor	Diagnostic Approach
Aquagenic urticaria	<ul style="list-style-type: none">• Water• Wheals occur within minutes of exposure	<ul style="list-style-type: none">• Wet clothes applied at body temperature for 20 min
Cholinergic urticaria	<ul style="list-style-type: none">• Increased body temperature in response to heat, exercise, spicy foods, and extreme emotion• Mediated by acetylcholine rather than histamine	<ul style="list-style-type: none">• Exercise and hot bath provocation
Contact urticaria	<ul style="list-style-type: none">• Contact with urticariogenic substance• Immunologic response to drugs, cosmetics, latex• Non-immunologic response to animals (jellyfish), plants (nettles), and chemicals	<ul style="list-style-type: none">• Prick/patch test read after 20 min
Exercise-induced urticaria	<ul style="list-style-type: none">• Physical exercise	<ul style="list-style-type: none">• Exercise test such as running in place

blanched centers. Individual lesions arise suddenly, typically resolve within 24 to 36 hours, and may continue to recur for an indefinite period of time. The lesions are usually extremely pruritic, but patients have also described a tingling or prickling sensation. The physical urticarias may present with a characteristic morphology and/or systemic symptoms in addition to the typical wheal and flare cutaneous reaction.

- A. Dermatographic Urticarial Lesions** are typically linear wheals occurring at the site of scratching or friction. The lesions appear rapidly and usually resolve within 30 minutes (Fig. 44-3).
- B. Delayed Pressure Urticaria** occurs as erythematous, deep, often painful, local swellings arising from 3 to 6 hours after sustained pressure to the skin. It may be associated with fevers, chills, arthralgias, and myalgias.
- C. Cold Urticaria** presents with a typical wheal and flare reaction at the site of contact with a cold substance and may be associated with headache, hypotension, syncope, wheezing, shortness of breath, palpitations, and gastrointestinal symptoms (Fig. 44-4).
- D. Cholinergic Urticaria** classically appears as small, monomorphic, 1- to 2-mm, pruritic wheals surrounded by large areas of erythema. The lesions may become confluent. Associated dizziness, headache, syncope, flushing, respiratory symptoms, and gastrointestinal symptoms may occur.

III. WORKUP In some cases, the type of urticaria and eliciting factor can be identified by a thorough history and physical examination as some of the physical urticarias present with a distinctive morphologic appearance. Obtaining a complete medication history is imperative and should include all prescription, over-the-counter, oral, and topical medications (new or old) as well as vitamins, supplements, and herbal medications. Medications such as aspirin, NSAIDs, antibiotics, and opiate analgesics are frequently the offending agent in urticaria. Patients should also be asked about recent viral illness or chronic infections in



Figure 44-3. Urticarial lesions resulting from dermatographism. (With permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 44-4. Cold urticarial with a well-defined, rectangular wheal resulting from ice cube application. (With permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

protected sites such as the sinuses, the dental cavity, and the gallbladder. If a physical urticaria is suspected, often a simple test can be done to confirm the diagnosis, and several suggestions for such tests are listed in Table 44-1.

In most patients with chronic urticaria, identifying the underlying cause proves difficult. Evaluation should include a complete blood count, erythrocyte sedimentation rate, thyroid function tests, assays for antimicrobial and anti-thyroid antibodies, cryoproteins in patients with cold urticaria, and antinuclear antibody test in patients with some cases. An elevated white blood cell count may indicate chronic infection, and imaging of the sinuses or dentition may be helpful. An elevated eosinophil count may be caused by drugs, foods, parasites, and atopy. Workup may include testing for chronic *Helicobacter pylori* infection as well. Testing stool for ova and parasites may be indicated if a parasitic infection is being considered.

Serum hypocomplementemia is typically not present in chronic urticaria. IgE levels are not helpful as levels in patients with chronic urticaria are the same as in the general population. Skin biopsy is usually not helpful in the diagnosis of acute, chronic, or physical urticaria, but it may be of use when ruling out other differential diagnoses including urticarial vasculitis. The utility of allergen skin testing is limited.

IV. TREATMENT The ideal treatment of urticaria involves identification and avoidance of the causal factor; however, this is not possible in a majority of cases. In cases where a cause has been identified, treating the underlying cause or lifestyle modifications aimed at avoiding triggers may be sufficient to eradicate disease. For example, in cases of drug-induced urticaria, the offending agent should be avoided completely or substituted for another class of drugs. Drugs that cause nonallergic hypersensitivity reactions, most commonly NSAIDs and angiotensin-converting enzyme inhibitors, can not only elicit urticaria but also aggravate preexisting chronic urticaria. When IgE-mediated food allergy is the cause of urticaria, patients should be instructed to modify their diet such that they avoid foods that may trigger symptoms. In cases where chronic infection has been identified such as *H. pylori* or chronic infections in protected locations, urticaria may resolve after treatment of the underlying infection. For the physical urticarias, avoidance of stimuli should be practiced where possible. Patients should be counseled about lifestyle modifications that will enable them to eliminate exposure to stimuli. For example, in delayed pressure urticaria and dermatographism, it is important to counsel patients that avoiding friction, distributing pressure over a broader area, or cushioning against pressure may prevent flares. Minimizing stress, over-heating, and alcohol consumption may be helpful for all types of urticaria.

In cases where a cause cannot be identified or patients continue to have symptoms despite lifestyle modifications, treatment focuses on therapies that provide symptomatic relief, often by reducing the effects of mast cell mediators on target organs. Antihistamines are the mainstay of therapy. First-line therapy should include non-sedating second-generation H1-blocking antihistamines at low starting dosage, where the dose can be increased until sufficient response is achieved. The non-sedating second-generation antihistamines may be used in combination with one another as well. If symptoms remain uncontrolled, addition of a first-generation H1-blocking antihistamine should be considered. Second-generation H1-blocking antihistamines are preferred as first-line therapy not only because they are non-sedating but also because of their rapid onset of action, prolonged duration of effect allowing once daily dosing in some cases, and ability to increase the dose without a greater risk of adverse events. For refractory cases, the second-generation antihistamines have been shown to be safe at doses up to fourfold higher than the recommended daily dose. First-generation H1-blocking antihistamines are not preferred due to their pronounced anticholinergic and sedating side effects that last longer than the antipruritic effects. Additionally, the first-generation antihistamines incur a greater risk of interacting with other medications including analgesics, hypnotics, sedatives, and mood-elevating drugs as well as alcohol. If the patient is still having an inadequate response, addition of H2-blocking antihistamines or leukotriene-receptor antagonists may be helpful. The leukotriene-receptor antagonists have shown limited benefit as monotherapy. These agents may be most helpful as adjunctive therapy in cases of autoimmune urticaria, hypersensitivity to food additives, and hypersensitivity to aspirin or NSAIDs. Table 44-2 provides a summary of the antihistamines including recommended dosing schedules, while Table 44-3 summarizes the leukotriene-receptor antagonists.

Adjunctive therapy with a variety of anti-inflammatory agents has been reported successful in some cases, but studies are limited. These drugs are

TABLE 44-2		Antihistamines for Urticaria	
Class	Generic (Trade) Name	Recommended Dose	Half-Life (hours)
First-generation (sedating) H1 antagonists	Diphenhydramine (Benadryl)	25–50 mg po q4–6h	4
	Hydroxyzine (Atarax, Vistaril)	25–75 mg po daily at bedtime 25–50 mg po q6–8h	20
	Chlorpheniramine (Aller-Chlor, Chlor-Trimeton)	4 mg po q4–6h Up to 12 mg po at bedtime	25
	Doxepin (Silenor)	10–50 mg po daily at bedtime	17
Second-generation H1 antagonists	Cetirizine (Zyrtec)	10 mg po once daily	7–11
	Loratidine (Claritin, Alavert)	10 mg po once daily	8–11
Newer second-generation H1 antagonists	Fexofenadine (Allerga)	180 mg po once daily 60 mg po twice a day	17
	Levocetirizine (Xyzal)	5 mg po once daily	7–10
	Desloratidine (Clarinex)	5 mg po once daily	19–35
H2 antagonists	Ranitidine (Zantac)	150 mg po twice a day	2–3
	Cimetidine (Tagamet)	400 mg po twice a day	2

TABLE 44-3		Leukotriene-Receptor Antagonists for Urticaria	
Generic (Trade) Name		Recommended Dose	
Montelukast (Singulair)		10 mg po once daily	
Zafirlukast (Accolate)		10–20 mg po twice a day	

TABLE 44-4 Alternative Therapies for Urticaria

- Prednisone
- Cyclosporine
- Dapsone
- Sulfasalazine
- Methotrexate
- Intravenous immunoglobulin
- Plasmapheresis
- Phototherapy
- Omalizumab

typically used only in cases of urticaria refractory to treatment with antihistamines. Table 44-4 provides a list of alternative agents that have been reported to be useful in some cases of urticaria. While corticosteroids may be useful, long-term therapy is discouraged. Low-dose therapy (10 mg daily) may reduce disease duration, but often, symptoms flare quickly when the drug is tapered. Cyclosporine, which inhibits histamine release from basophils and partially inhibits release of mast cell mediators, is another reasonable alternative. A few case-controlled studies have demonstrated the effectiveness of low-dose cyclosporine (3 to 6 mg/kg/day); however, its use is limited by the drug's side-effect profile. The evidence for the use of dapsone, sulfasalazine, methotrexate, intravenous immunoglobulin, and plasmapheresis is limited to noncontrolled studies and case series. Phototherapy reduces the number of mast cells in the skin and may be helpful in resistant cases of urticaria. Although cold urticarial can be treated with antihistamines, treatment with cyproheptadine 4 to 8 mg three to four times per day seems to be particularly effective.

Omalizumab is a recombinant humanized monoclonal antibody that binds to circulating IgE. There have been two, multicenter, randomized, placebo-controlled trials as well as several case series and case reports showing omalizumab to be effective and well tolerated in chronic spontaneous urticaria. It has also been shown to be helpful in refractory cases of dermatographism as well as cholinergic, solar, cold, heat, and delayed pressure urticaria. Some studies have shown complete remission with a single dose of omalizumab; however, more studies are needed in order to determine the appropriate dosing schedule. Current literature suggests that 150 to 300 mg of omalizumab every 4 weeks is sufficient in most patients.

In addition to medical therapy, there are several options for local measures that may help improve the symptoms of urticaria. Cold water compresses or ice packs may provide symptomatic relief for pruritus, although this would not be recommended for cases of cold urticaria. Tepid baths with colloidal oatmeal may also be helpful. Topical preparations containing menthol, phenol, pramoxine, or benzyl alcohol may relieve pruritus, and these include products such as Eucerin anti-itch cream, Sarna lotion, and calamine lotion.

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Suggested Readings

- Goldsmith LA, Katz SI, Gilchrest BA, eds. *Fitzpatrick's Dermatology in General Medicine*. 8th ed. New York. The McGraw-Hill Companies; 2012:414-430.
- Metz M, Maurer M. Omalizumab in chronic urticaria. *Curr Opin Allergy Clin Immunol*. 2012;12:406-411.
- Ortonne JP. Urticaria and its subtypes: the role of second-generation antihistamines. *Eur J Intern Med*. 2012;23:26-30.
- Schaefer P. Urticaria: evaluation and treatment. *Am Fam Physician*. 2011;83(9):1078-1084.
- Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA²LEN/EDF/WAO guideline: definition, classification and diagnosis of urticarial. *Allergy*. 2009;64:1417-1426.
- Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA²LEN/EDF/WAO guideline: management of urticaria. *Allergy*. 2009;64:1427-1443.

VASCULAR TUMORS

Infantile Hemangiomas

I. BACKGROUND Infantile hemangiomas are the most common soft-tissue tumors of infancy, occurring in approximately 10% of the population (Fig. 45-1). The etiology is unknown, but identifiable risk factors include female sex, premature birth, low birth weight, and fair skin. They consist of rapidly dividing benign endothelial cells.

II. CLINICAL PRESENTATION Infantile hemangiomas typically present during the first few weeks to months of life. The morphology depends on the depth within the skin. Superficial hemangiomas present as well-demarcated, finely lobulated, bright red papules/plaques, while deep hemangiomas present as a soft, ill-defined subcutaneous faint blue masses. There are often components of both. They follow a characteristic growth pattern of rapid growth in the first few weeks, followed by a period of slower growth between 6 and 12 months of age, followed by a slow involution. The exact time frame for growth and involution is difficult to predict. In general, 30% involute by the age of 3, and an additional 10% involute each additional year of life (i.e., 40% by age 4, 50% by age 5, and 90% by age 9).

III. WORKUP Most infantile hemangiomas do not require any workup. Doppler ultrasound can help confirm the diagnosis if not evident clinically. Extracutaneous disease is associated with certain anatomical sites and therefore may require some additional workup. Large facial hemangiomas may be associated with other congenital anomalies in PHACES syndrome (posterior fossa defects, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, eye abnormalities, and sternal/supra-abdominal clefting). These patients should be sent for ophthalmologic examination, echocardiogram, and a magnetic resonance imaging (MRI)/magnetic resonance angiography of the head and neck (Table 45-1). Lumbosacral hemangiomas may be associated with genitourinary anomalies such as an imperforate anus, renal anomalies, and underlying spinal cord anomalies. High-resolution ultrasound or MRI should be done to look for spinal cord involvement. If numerous lesions are present at birth, there is an increased risk of visceral lesions, particularly liver and gastrointestinal tract. Liver ultrasound and stool guaiac should be performed.

IV. TREATMENT The prognosis of the vast majority of infantile hemangiomas is excellent. Spontaneous involution is the typical outcome, so most infantile hemangiomas do not need any treatment. There are several exceptions.



Figure 45-1. Infantile hemangioma. (From Rubin E, Farber JL. *Pathology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.)

TABLE 45-1 Hemangiomas with Suspected Congenital Anomalies		
Location	Possible Anomaly	Workup
Large facial hemangioma	PHACES syndrome	Ophthalmologic evaluation Cardiac evaluation MRI/MRA of head and neck
Lumbosacral hemangioma	GU anomalies	MRI of spinal cord
Numerous hemangiomas	Visceral lesions	Liver ultrasound Stool guaiac

PHACES, posterior fossa defects, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, eye abnormalities, and sternal/supra-abdominal clefting; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; GU, genitourinary.

Involution of the vascular component does not always result in completely normal skin, as larger, exophytic hemangiomas leave residual fibrofatty scarring that can be disfiguring. Astigmatism, strabismus, and amblyopia can result from periocular skin involvement. Hemangiomas involving the mandible, chin, and upper neck may be associated with airway involvement and respiratory distress. Ulceration is the most common complication, which can result in scarring, pain, and potentially infection. Up until recently, oral and intralesional corticosteroids have been the mainstay of treatment. However, the use of systemic β -blockers has been proven to be a potentially safer and more effective treatment alternative. Over 90% of patients have dramatic reduction in the size of their hemangiomas as early as 1 to 2 weeks after initiation of treatment. There are currently no consensus guidelines regarding the use of propranolol for the treatment of

hemangiomas, and studies to determine the optimal dosing and monitoring are ongoing. Topical β -blockers such as timolol have also been found to be of use. Vincristine, recombinant interferon- α , pulsed dye laser, Nd:YAG, and surgical excision are other treatment options for treatment-resistant lesions.

Congenital Hemangiomas

I. BACKGROUND Congenital hemangiomas are much less common than infantile hemangiomas. They are present at birth and classified as either rapidly involuting congenital hemangioma (RICH) or noninvoluting congenital hemangioma (NICH), which never involutes at all.

II. CLINICAL PRESENTATION They typically present as pink to violaceous masses with overlying coarse telangiectasias, surrounded by a pale rim. RICHs are characterized by rapid involution over the first year of life, while NICHs grow proportionately with the child.

III. WORKUP Doppler ultrasound may be used to confirm the diagnosis.

IV. TREATMENT Surgical excision.

Kaposiform Hemangioendothelioma

I. BACKGROUND Kaposiform hemangioendotheliomas (KHs) are rare vascular tumors that typically present during the first months to 1 year of life. They are one of the major causes (in addition to tufted angiomas) of Kasabach-Merritt phenomenon (KMP), a coagulopathy characterized by thrombocytopenia.

II. CLINICAL PRESENTATION KHs present as rapidly enlarging, subcutaneous, ecchymotic masses. They often become more indurated and enlarged when the coagulopathy develops. Residual masses often persist even after the coagulopathy resolves.

III. WORKUP Complete blood count (CBC) should be closely monitored, as thrombocytopenia is a common complication.

IV. TREATMENT There is no routinely effective treatment. Corticosteroids, interferon- α , vincristine, cyclophosphamide, aspirin, dipyridamole, vincristine, excision, embolization, and radiation therapy have all been used with variable success. KMP is a potentially life-threatening emergency. Platelet transfusions may lead to enlargement of the tumor and worsening of the coagulopathy.

Pyogenic Granuloma

I. BACKGROUND Pyogenic granulomas are common vascular tumors that may develop spontaneously or in response to trauma.

II. CLINICAL PRESENTATION They present as a rapidly growing, friable, red, vascular papule, or nodule usually located on the extremities that bleeds profusely and repeatedly with minimal trauma. They often have a peripheral collarette of scale (Fig. 45-2).



Figure 45-2. Pyogenic granuloma. (From Fleisher GR, Ludwig S, Baskin MN. *Atlas of Pediatric Emergency Medicine*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

III. WORKUP The tissue should be sent for pathology to rule out other mimicking neoplasms.

IV. TREATMENT Shave excision followed by light electrocautery of the base.

Cherry Angioma

I. BACKGROUND Cherry angiomas are the most common of the acquired cutaneous vascular proliferation that typically appear in peoples in their 30s and after. They consist of ectatic capillaries and postcapillary venules in the dermis.

II. CLINICAL PRESENTATION They present as bright red dome-shaped papules ranging from pinpoint size up to ~10 mm in diameter, most commonly on the trunk and proximal extremities.

III. WORKUP No workup is required.

IV. TREATMENT Treatment is not necessary, but may be requested for cosmetic purposes or because of chronic trauma and bleeding. Shave excision, electrodessication, and laser ablation are all effective options.

VASCULAR MALFORMATIONS

Vascular malformations consist of ectatic vascular anomalies secondary to errors in vascular morphogenesis. They are present at birth, but often worsen over time. They are classified by the type of vessels involved, but are frequently made up of more than one vessel type. Treatment is very individualized, and the best

TABLE 45-2 **Classification of Vascular Anomalies**

Vascular Tumors	Vascular Malformations
Infantile hemangioma	Capillary malformations
Congenital hemangioma	Venous malformations
Tufted angioma	Lymphatic malformations
Kaposiform hemangioendothelioma	Arteriovenous malformations
Pyogenic granuloma	

management is often provided by a vascular malformation multidisciplinary team, which exist at many academic centers (Table 45-2).

Capillary Malformations

Nevus Simplex ("Salmon Patch")

- I. BACKGROUND** Nevus simplex is the most common vascular anomaly of infancy.
- II. CLINICAL PRESENTATION** They present as a pink to red vascular patch often involving the glabella, eyelids, perinasal area, and nape of the neck. With the exception of the neck, they typically fade by 2 years of age (Fig. 45-3).
- III. WORKUP** No workup is required.
- IV. TREATMENT** No treatment is necessary; however, pulsed dye laser can be used for persistent lesions.



Figure 45-3. Nevus simplex ("salmon patch"). (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

Port Wine Stains

- I. BACKGROUND** Port wine stains (PWSs) consist of dilated capillaries within the upper dermis that are present at birth. They are occasionally associated with underlying lymphatic malformations (LMs) or venous malformations (VMs) and may be associated with other congenital abnormalities such as Sturge-Weber syndrome and Klippel-Trenaunay syndrome (KTS). The risk of Sturge-Weber syndrome (PWS, cerebral vascular malformations, and ophthalmologic disease) associated with PWS involving the V1 branch of the trigeminal nerve is approximately 10% to 25%. The risk increases for bilateral V1 PWS (>50%). PWSs involving the lumbosacral back may be associated with underlying spinal vascular anomalies or a tethered spinal cord. KTS consists of a capillary VM associated with progressive overgrowth of the affected extremity.
- II. CLINICAL PRESENTATION** In infancy, PWSs are pink, flat vascular patches. Over time, the affected blood vessels become more ectatic, leading to a more red to purple color and a more papular to nodular texture (Fig. 45-4).
- III. WORKUP** An ophthalmology consult and MRI of the brain should be done if V1 is involved. Limb lengths should be monitored if an extremity is involved, and an MRI can delineate the extent of soft tissue and bone involvement. An MRI of the spine should be done to rule out spinal dysraphism if there is lumbosacral involvement.
- IV. TREATMENT**
- A. Lasers (Pulsed Dye, Nd: YAG, KTP).** Often requires up a minimum of six to eight treatments. Lesions may slowly recur. Timed epiphysiodesis can be used to avoid a leg-length discrepancy in patients with KTS.



Figure 45-4. Port wine stain. (From Weber J, Kelley J. *Health Assessment in Nursing*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

Venous Malformations

- I. BACKGROUND** VMs are composed of ectatic, tortuous venous channels within the skin and often extend into the surrounding mucosa, soft tissue, muscle, and bone. They can be isolated or part of a syndrome. Multiple VMs and asymmetric enchondromas may develop in patients with Maffucci syndrome. Blue rubber bleb nevus syndrome (BRBNS) consists of multiple cutaneous VMs associated with submucosal vascular anomalies of the gastrointestinal tract. VMs are often associated with a chronic intravascular coagulopathy and associated pain.
- II. CLINICAL PRESENTATION** Soft, ill-defined, bluish cutaneous, or subcutaneous masses typically present at birth. They often become more evident when the involved area is put into a dependent position. VMs are often described as a “bag of worms” texture caused by the multiple dilated veins within the lesion.
- III. WORKUP** MRI is the best imaging modality for defining the extent of involvement. A CBC should be monitored in patients with BRBNS as gastrointestinal lesions often result in iron deficiency anemia. An elevated D-dimer is seen in patients with an associated intravascular coagulopathy.
- IV. TREATMENT** Surgical excision, embolization, laser (Nd:YAG, KTP), and sclerotherapy have all been used with varying success. Treatment often requires multiple modalities and multiple procedures over the course of the patients’ life. Elastic compression garments may help to reduce swelling and pain. Low molecular weight heparin and low-dose aspirin may be beneficial in patients with an associated coagulopathy.

Lymphatic Malformations

- I. BACKGROUND** LMs result from congenital hyperplasia of the lymphatic network. They may be microcystic, macrocystic, or some combination of both. They can be superficial or deep. Superficial microcystic lesions are historically described as “lymphangioma circumscriptum” and deep macrocystic malformations as “cystic hygromas” (Figs. 45-5 and 45-6).
- II. CLINICAL PRESENTATION** Macrocystic LMs present as painless, soft, flesh-colored to slightly translucent, fluid-filled masses, most commonly involving the neck or axilla. Deeper lesions may involve the underlying muscle and bone. The mucosa and airway may also be involved. Microcystic LMs present as a collection of flesh-colored vesicular papules, usually with focal red to black hemorrhagic areas, often described as “frog spawn.” Affected areas are more prone to developing infections, and the resulting inflammation results in an expansion of the LM.
- III. WORKUP** The diagnosis can be confirmed by ultrasound. MRI is best for defining the extent of the lesion.
- IV. TREATMENT** Surgical excision can be done for well-localized areas. Compression garments may limit complications and infections. Sclerotherapy



Figure 45-5. Microcystic lymphatic malformation. (From Fleisher GR, Ludwig W, Baskin MN. *Atlas of Pediatric Emergency Medicine*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)



Figure 45-6. Macrocytic lymphatic malformation. (From Fleisher GR, Ludwig W, Baskin MN. *Atlas of Pediatric Emergency Medicine*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)

is more effective for macrocystic lesions. Superficial lesions may improve with laser treatments (CO₂, Nd:YAG, diode). Transient, intermittent swelling typically responds to nonsteroidal anti-inflammatory drugs, corticosteroids, and antibiotics.

Arteriovenous Malformations

I. BACKGROUND Arteriovenous malformations (AVMs) are rare fast-flow vascular malformation consisting of a direct connection between arteries and veins without an intervening capillary bed. They are potentially life-threatening secondary to massive bleeding and high output cardiac failure. Associated syndromes include Cobb syndrome, Parkes-Weber syndrome, Bonnet-Dechaume-Blanc syndrome, Bannayan-Riley-Ruvalcaba syndrome, and Cowden syndrome.

II. CLINICAL PRESENTATION The head and neck area are most commonly involved. At birth, AVMs often look similar to a PWS. They may be slightly warm to touch, and there may be a faint thrill or bruit appreciated. As they progress, the vascular lesions enlarge, darken, and begin to invade deeper structures. They become a deeper red color, and the thrill becomes more prominent. As it continues to progress, AVMs can become ulcerated and painful.

III. WORKUP Ultrasound and MRI can confirm the diagnosis and delineate the extent of the lesion.

IV. TREATMENT Treatment of AVMs is difficult. Preoperative embolization prior to surgical excision is often necessary in order to intraoperative bleeding.

Suggested Readings

- Enjolras O. Vascular malformations. In: Bologna JL, Jorizzo JL, Schaffer JV, eds. *Dermatology*. 3rd ed. London: Elsevier Limited; 2012:1711-1728.
- Frieden IJ. Vascular tumors and malformations. In: Rudolph CD, Rudolph AM, Hostetter MK, Lister G, Norman J, eds. *Rudolph's Pediatrics*. 21st ed. New York, New York: McGraw-Hill; 2003:1204-1209.
- Garzon MC, Huang, JT, Enjolras O, et al. Vascular malformations part 1. *J Am Acad Dermatol*. 2007;56(3):353-370. Review.
- Haggstrom AN, Garzon MC. Infantile hemangiomas. In: Bologna JL, Jorizzo JL, Schaffer JV, eds, *Dermatology*. 3rd ed. Elsevier; 2012:1691-1709.
- Richter GT, Friedman AB. Hemangiomas and vascular malformation: current theory and management. *Int J Pediatrics* 2012 (2012). Article ID 645678.

I. BACKGROUND Vitiligo is a common acquired pigmentary disease affecting 1% to 2% of the population. Localized or generalized areas of the skin become completely depigmented as melanocytes are selectively destroyed. This finding is in contrast to albinism, in which melanocytes are present but there is little or no pigmentation because of faulty or absent melanin synthesis. The exact cause of vitiligo remains unknown. Because of the association with other autoimmune diseases, an autoimmune etiology is favored.

Vitiligo appears to have a familial incidence of 20% to 30% and is found with increased frequency in patients with endocrinopathies. These include thyroid disease such as Hashimoto thyroiditis and Graves disease, other endocrinopathies such as Addison disease, gonadal atresia, and diabetes mellitus. In patients with vitiligo, there is also an increased incidence of halo nevi, pernicious anemia, alopecia areata, and ocular abnormalities. Complete spontaneous repigmentation is rare.

II. CLINICAL PRESENTATION Onset of vitiligo is typically seen in ages 10 to 30, and rarely in infancy or old age. The lesions of vitiligo appear as white or depigmented macules or patches, usually with sharp borders and are found symmetrically over bony prominence such as the hands, forearms, feet, and around body orifices (lips, eyes, and anogenital areas) (Figs. 46-1–46-3). Lesions begin ranging from millimeters in size but can enlarge centrifugally at an unpredictable rate. Injury to the skin of these patients may cause a temporary or permanent loss of pigment in that area (Koebner phenomenon). Scars, scratch marks, and bruises may therefore heal with no pigment present. Hair growing from vitiliginous skin may be depigmented. There are no symptoms associated with the depigmentation of vitiligo. These areas, however, sunburn easily.

There are three subtypes of vitiligo: localized, generalized, and universal. Localized vitiligo involves less than 20% of the body surface area. It can be either focal, presenting as one of more macules in one area, most commonly in the distribution of the trigeminal nerve; or segmental, presenting in a dermatomal pattern. Segmental vitiligo is much more common in children than adults and tends to spread rapidly within the segment of skin (Fig. 46-4). This subtype is rarely associated with autoimmune or endocrine disorders. Generalized vitiligo can be found in more than one isolated area, usually acrofacial (involving distal fingers and around orifices) and/or widely scattered throughout the body. Universal vitiligo describes complete or near-complete depigmentation (Fig. 46-5). It is often associated with endocrinopathies.

III. WORKUP The diagnosis of vitiligo is usually made with clinical observation (Table 46-1). A Wood lamp examination may be helpful to accentuate the vitiligo patches from normal skin, especially in fair skin. At times biopsies

TABLE 46-1 **Differential Diagnosis**

- Addison disease
- Chemical leukoderma (from phenolic germicidal household chemicals)
- Idiopathic guttate hypomelanosis
- Leprosy
- Mycosis fungoides
- Piebaldism
- Pityriasis alba
- Postinflammatory depigmentation
- Steroid-induced hypopigmentation
- Scleroderma
- Tinea versicolor
- Tuberous sclerosis



Figure 46-1. Vitiligo in periocular distribution. Note the white eyelashes. (From Goodheart HP: *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 46-2. Vitiligo on the forearm. Neutrogena Skin Care Institute. (Sauer GC, Hall JC. *Manual of Skin Diseases*. 7th ed. Philadelphia, PA: Lippincott-Raven; 1996.)



Figure 46-3. Vitiligo on hands.

may be required to rule out other causes of depigmentation and hypopigmentation. Histology shows complete absence of melanocytes and epidermal pigmentation.

Given the association with other disorders, particularly thyroid disease, diabetes, pernicious anemia, and autoimmune disorders, patients need to be



Figure 46-4. Segmental vitiligo. (Image provided by Stedman's.)



Figure 46-5. Extensive vitiligo. The residual normal pigmentation was eventually removed with MBEH. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

TABLE 46-2	Laboratory Workup
Biopsy	
CBC (complete blood count)	
ANA (anti-nuclear antibody)	
TSH (thyroid stimulating hormone)	
Fasting glucose	

screened periodically. TSH, CBC, ANA, and fasting blood glucose levels should be checked upon initial diagnosis (Table 46-2).

IV. TREATMENT Treatment outcomes are highly variable and unpredictable. For each option, the health risks, financial and time cost, and the patient’s emotional trauma must be weighed against the potential benefits for each individual patient. Regardless, all patients with vitiligo should practice aggressive sun protection measures. Avoidance of the sun during peak hours and conscientious use of broad-spectrum sunscreens should be stressed in all patients (Table 46-3).

- A. Topical Nonsteroidals.** Nonsteroidal immunomodulators such as tacrolimus ointment 0.1% may induce some repigmentation in up to 90% of patients. Application of the ointment twice daily for 2 months has been shown to be nearly as effective as superpotent topical corticosteroids and does not carry with it the risk of adverse effects. As such, it may be used as first-line agent in most vitiligo cases involving small affected areas, especially the head and neck. Some have observed similar results using pimecrolimus 1% cream. Vitamin D analogs such as calcipotriol can influence melanocyte maturation and have also led to some successful treatments. Any of them may be used in combination with UV-B or excimer laser to improve the efficacy of phototherapy.
- B. Steroids.** Topical and intralesional corticosteroids have yielded very mixed results in the treatment of vitiligo, although for localized lesions, a trial of a potent topical steroid administered twice a day is worthwhile. It often becomes treatment of first choice due to its low cost, convenience, and ease of use. The potential adverse reactions—particularly atrophy, glaucoma (if used near the eyes), and, for intralesional therapy, treatment-related depigmentation—must be kept in mind. Topical treatment is continued

TABLE 46-3	Primary Treatment Options
1. Topical immunomodulators (tacrolimus and pimecrolimus)	
2. Topical steroids	
3. Phototherapy (narrowband UV-B, PUVA, and excimer laser)	

for 3 to 4 months, but should be abandoned if no repigmentation is seen. Although oral steroids may be helpful, it is a poor long-term strategy given the risks and toxicity. Low-dose oral corticosteroids (0.3 mg/kg/day) over a 4-month course were found to be helpful in patients with actively spreading vitiligo.¹

- C. Narrowband UVB (NB-UVB).** This method of phototherapy at 310- to 315-nm wavelength has demonstrated effectiveness as monotherapy and now widely used. The initial starting dose is approximately 300 mJ/cm², with increments of 10% to 20% at each subsequent exposure. Treatment is administered 2 to 3 days a week. The advantages of NB-UVB over PUVA (see below) include shorter treatment times; no drug costs; reduced phototoxic reactions; and reduced risk in children, pregnant women, and patients with hepatic and kidney dysfunction compared with the traditional UVA and psoralen combination (PUVA). NB-UVB has become the phototherapy of first choice in generalized vitiligo.
- D. Excimer Laser.** This is an intense NB-UVB light at a wavelength of 308 nm. This has proven to be effective, safe, and well tolerated. However, the results are temporary and must be maintained with retreatment. Patients are treated twice a week for at least 20 sessions. Moreover, given the time-consuming nature of targeting each individual lesion with a discrete laser beam, the excimer laser is practical only in cases of limited involvement. Some have reported faster response when combining excimer laser with topical tacrolimus.
- E. Psoralen Plus Ultraviolet A.** Systemic psoralen plus phototherapy attempts to repigment skin with the topical or systemic use of psoralen compounds. As a general guide, if the vitiliginous skin is <6 cm² (the size of a quarter or half-dollar), topical psoralens may be used; if a large portion of the body surface is involved, systemic psoralens are indicated; if the area involved is extremely widespread (>50% of the body surface area), depigmentation with 20% monobenzy ether of hydroquinone (MBEH) may be considered. PUVA is particularly useful in skin types IV–VI.

Psoralen compounds are tricyclic furocoumarin-like molecules that radically increase the erythema response of skin to long-wave ultraviolet light (UVA) after either topical application or systemic administration. The most commonly used oral psoralen is 8-methoxypsoralen (8-MOP). 8-MOP (Oxsoresalen-Ultra) at a dose of 0.4 to 0.6 mg/kg, taken at least 1 hour before carefully monitored indoor UVA light source, achieves some repigmentation in 70% of patients. Pigment reappears first as dots around hair follicles and then spreads slowly, becoming confluent. Dots of pigment should be seen within 25 exposures with facial lesions and 50 exposures with involvement elsewhere; if not, treatment should be discontinued. Patients should be instructed to wear UV-protective sunglasses before and after exposure on treatment days. Following treatment, a sunscreen effective against UVA should be applied to all exposed skin; this will provide partial protection. Prolonged exposure to sunlight beyond the treatment period should be avoided for 8 hours after the medication has been ingested. Nontender, minimal pink coloration of the patches of vitiligo is acceptable, but if increasing redness develops, discontinue treatment until only faint pinkness remains.

Therapy must be initiated gradually and monitored carefully. Treatments should be given one to two times weekly and never for 2 days in a row. To be successful, therapy must continue for 9 to 18 months. The age of the patient and duration of vitiligo do not affect the response rate. Seventy-five percent of patients will have partial repigmentation when treated twice a week for more than a year. Lesions on the face and neck repigment more easily than those over an osseous prominence such as the dorsa of the hands, the elbows, and the knees. If treatment is discontinued before an area has completely filled in, the lesion is likely to gradually become white again.

PUVA may be administered using topical psoralen as well, either using a psoralen solution or a cream (0.1% to 0.3% 8-MOP), followed by UVA exposure. The topical agent is applied to the affected area of the body to be treated for 30 minutes. The initial dose of UVA for topical PUVA for all skin types is 0.3 J/cm². The frequency is one to two times a week. As in the case for oral psoralen, additional UV exposure via sunlight should be avoided after topical PUVA treatment to minimize the risk of solar damage.

Psoralens may produce pruritus, nausea, corneal burns, and an acute and painful erythema. Long-term therapy with PUVA may produce premature aging, cataracts, photoallergic dermatitis, freckling of the skin, and an increased risk of skin cancer, including melanoma.

F. Depigmentation. Depigmenting the surrounding skin to blur the margins of the lesion or removing all remaining pigmentation in extensive cases may lead to cosmetic improvement. Blurring of the margins of the lesion may be attempted with hydroquinone compounds. Permanent removal of all remaining pigment requires the use of 20% MBEH cream. MBEH is melanocidal. It is selectively taken up by melanocytes and metabolized into free radicals that can destroy melanocytes permanently, leading to irreversible depigmentation. As a result, MBEH is usually reserved for generalized depigmentation in patients with extensive vitiligo and should not be used under any other circumstances. This process requires up to 12 months of continuous twice-daily application to achieve complete depigmentation. The patient needs to understand the permanence of this procedure and counseled appropriately of the potential emotional and social consequences.

- G. Camouflage.** Patients should be informed that medications are not the only solution. Several cover-up products offer excellent cosmesis if applied properly. Some brands include Covermark, Dermablend, Dy-O-Derm, and Vitadye. An aloe-based synthetic melanin product (Melasyn) is helpful in covering depigmented areas of vitiligo. This product offers protection against UV light and can be made waterproof by applying a spray-on sealant.
- H. Surgery.** Epithelial sheet grafting (after dermabrasion or suction blister formation) minigrafting, and the “flip-top” procedure have been successful in stable vitiligo patients.² However, given the cost and the time-consuming nature, these techniques are only appropriate for small areas. Patients should also be cautioned that surgery may lead to scarring and color mismatch and hyperpigmentation, in addition to koebnerization, which may exacerbate vitiligo. Most recently, the EpiGraft system by Momelan promises to dramatically speed up the epidermal grafting procedure, while reducing the pre- and post-procedure discomfort and promote rapid recovery.

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REFERENCES

1. Kim SM, Lee H-S, Hann S-K. The efficacy of low-dose oral corticosteroids in the treatment of vitiligo patients. *Int J Dermatol*. 1999;38:546-550.
2. McGovern TW, Bologna J, Leffell DJ. Flip-top pigment transplantation: a novel transplantation procedure for the treatment of depigmentation. *Arch Dermatol*. 1999;135(11):1305-1307.

Suggested Readings

- Guerra L, Capurro S, Melchi F, et al. Treatment of “stable” vitiligo by timed surgery and transplantation of cultured epidermal autografts. *Arch Dermatol*. 2000;136:1380-1389.
- Halder RM, Young CM. New and emerging therapies for vitiligo. *Dermatol Clin*. 2000;18:79-89.
- Nijoo MD, Bos JD, Westerhof W. Treatment of generalized vitiligo in children with narrow-band (TL-01) UVB radiation therapy. *J Am Acad Dermatol*. 2000;42:245-253.
- Nijoo MD, Westerhof W, Bos JD, et al. The development of guidelines for the treatment of vitiligo. *Arch Dermatol*. 1999;135:1514-1521.

I. BACKGROUND Warts are intraepidermal tumors of the skin and mucosa caused by infection with the human papillomavirus (HPV), a group of nonenveloped, double-stranded DNA viruses. These papillomaviruses are host specific; there are over 100 variants known to cause disease in humans. Implantation of HPV into basal keratinocytes is thought to occur primarily through mechanical disruption of the skin barrier. The virus replicates in the nucleus of the keratinocyte as it differentiates and migrates upward through the epidermis. Once the entire nuclear space is filled, virus spills into the cytoplasm; in the stratum corneum, the virus lies free within the keratin mass. HPV, a very stable virus, is shed from the superficial keratinocytes and then transmitted through hetero- or autoinoculation and even through indirect contact with contaminated articles such as swimming pool surfaces.

Although difficult to cultivate in vitro, in situ DNA hybridization, polymerase chain reaction, and molecular nucleic acid hybridization have allowed the separation and cloning of many HPV subtypes (Table 47-1). Infections by HPV subtypes show a marked preference for specific sites and are often characterized by type-specific macroscopic and microscopic features. Several HPV types are oncogenic, and there is a strong association between certain types, particularly HPV-16 and -18, and dysplasias and invasive cancers of the female lower genital tract, the penis, and the anorectal region.

HPV lesions are more common in patients receiving immunosuppressive drugs and those with immune deficiency states, including lymphoma, chronic lymphocytic leukemia, Hodgkin disease, and human immunodeficiency virus (HIV). This information, plus the increased frequency of cell-mediated responses and antibodies specific for viral antigens in patients with regression or cured warts, supports a role for immunity in the resolution of warts. Most HPV infections are latent or transient, suggesting intracellular control of viral expression; when this control is compromised, HPV-associated diseases will result. In persons with a healthy immune system, approximately 20% to 30% of all lesions will involute spontaneously within 6 months, 50% within 1 year, and 66% within 2 years. New lesions may continue to appear during this period and are seen three times more frequently in children with warts than in those without.

II. CLINICAL PRESENTATION Clinically, warts are classified by location into three main subtypes: cutaneous, anogenital/mucosal, and epidermodysplasia verruciformis (EV). There are several morphologic variants of warts such as the following:

A. Common Warts start as small, pinhead-sized, flesh-colored, translucent papules and grow over several weeks or months to larger, raised, papillary-surfaced, flesh-colored or darker, hyperkeratotic papules. Black specks of hemosiderin pigment may be seen in thrombosed capillary loops (Fig. 47-1).

TABLE 47-1 Human Papillomavirus Subtypes

Lesions	HPV Types
Common, palmar, plantar, myrmecia, and mosaic warts	1, 2, 4
Flat warts	3, 10
Butcher's warts	2,7
Digital squamous cell carcinoma, Bowen disease	16
EV	3, 5, 8
EV squamous cell carcinoma	5
Condylomata acuminata	6, 11
Intraepithelial neoplasias (cervical condyloma plana, bowenoid papulosis, erythroplasia of Queyrat)	16
Buschke-Lowenstein tumor	6, 11
Recurrent respiratory papillomatosis, conjunctival papillomas	6, 11
Heck disease	13, 32

EV, epidermodysplasia verruciformis; HPV, human papillomavirus.



Figure 47-1. Common warts. Lesions demonstrate the loss of normal skin markings. “Black dots” or thrombosed capillaries are pathognomonic. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

Paring the lesion may result in punctate bleeding points. Common warts are found most often on the hands, especially in children, or on other sites often subjected to trauma. They may grow anywhere on the epidermis or mucous membranes and are spread by contact or autoinoculation. Common warts are most frequent between the ages of 12 and 16.

- B. Filiform Warts** are slender, soft, thin, finger-like growths seen primarily on the face and neck.
- C. Flat, Plane, or Juvenile Warts** are flesh-colored or tan, soft, 1- to 3-mm-diameter, discrete papules appearing primarily on the face, neck, extensor aspect of the forearms, and hands (Fig. 47-2).
- D. Plantar or Palmar Warts** are hyperkeratotic, firm, and elevated or flat lesions that interrupt the natural skin lines (as opposed to calluses). Red or black capillary dots may be seen. A mosaic wart (Fig. 47-3) consists of the confluence of multiple lesions into one large, usually flat lesion. As a point of contrast, corns or calluses are often more painful with direct pressure, whereas warts are more painful with lateral pressure.
- E. Warts That Grow in Warm, Moist, Intertriginous Areas** develop into soft, friable, vegetating clusters. These condylomata acuminata are found frequently on the foreskin and penis, particularly in uncircumcised men, on vaginal and labial mucosa, and in the urethral meatus and perianal area (Fig. 47-4).
- F. EV** is a chronic autosomal recessive disorder associated with chronic infection with HPV. The lesions can resemble tinea versicolor-like plaques or flat-topped papules. The lesions usually start in childhood and are often distributed on the face and extremities. During the third and fourth decades of life, one-third of patients will develop actinic keratoses and



Figure 47-2. Flat warts. Lesions are slightly elevated papules to the color of the patient's skin. Note the linear configuration resulting from autoinoculation of lesions on the bridge of this child's nose. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 47-3. Mosaic plantar warts. Note the clustering, “kissing lesions” on this patient’s toes. (From Goodheart HP. *Goodheart’s Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



Figure 47-4. Condyloma acuminatum. Lesions resemble small cauliflowers. (From Goodheart HP. *Goodheart’s Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

nonmelanoma skin cancers in sun-exposed areas. Ultraviolet light is involved in the pathogenesis of EV through its immunosuppressive and mutagenic effects.

III. WORKUP The diagnosis of a wart is usually made with clinical observation. With atypical lesions, biopsy may aid in diagnosis. Smaller genital warts may be hyperpigmented (resembling seborrheic keratoses or nevi).

Application of a 5% acetic acid solution for 10 to 15 minutes will turn possible verrucae white. Two-thirds of women and one-third of men with genital warts may have accompanying genital infections that must be identified and treated.

In the case of generalized verrucosis, which has been defined as cutaneous HPV infection presenting with greater than 20 lesions distributed in more than one localized region of the body, or if limited to acral distribution, affecting a majority of the digits, further work may reveal underlying immune deficiency states, including but not limited to EV, WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome, WILD (warts, immunodeficiency, lymphedema, dysplasia) syndrome, severe combined immunodeficiency syndrome, common variable immunodeficiency syndrome, hyper-IgM syndrome, hyper-IgE syndrome, atopic dermatitis, HIV, and chronic lymphocytic leukemia.¹ Leukopenia evaluation through a complete blood cell count, evaluation of specific lymphopenias through white blood cell differential, immunoglobulinemia evaluation with serum protein electrophoresis, and HIV status testing should all be considered.

IV. TREATMENT A multitude of therapeutic strategies for treatment of warts exist, with no one therapy universally preferred. Location, size, type, and number of warts merit consideration in choice of therapy, along with patient pain tolerance, patient preference, and physician preference. It is important to remember that warts are benign cutaneous growths and that the therapy should also be benign. Therapy should present no hazard to the patient, no scarring should result, and side effects should be minimal. It should be remembered that majority of warts resolve without treatment and even after treatment often recur. Yet for those causing significant pain, pruritus, or unsightliness, fortunately most lesions can be treated successfully with persistence.

Although not shown to treat genital warts, it is worthwhile to mention that quadrivalent (Gardasil) HPV vaccines not only protects against HPV types 16 and 18, implicated in majority of cervical cancers, but also protects against HPV types 6 and 11, which are causative in 90% of genital warts.² It is given in a three-dose series (second dose 1 to 2 months and third dose 6 months after first) and is recommended for 11- and 12-year-old boys and girls, but can be given as early as 9 years old.² Vaccination is also recommended for 13- through 21-year-old males and 13- through 26-year-old females who have not completed the vaccine series.

Meta-analysis of randomized clinical trials highlights that largely due to inadequacy of study designs and the high rate of spontaneous cure, there exists a paucity of evidence-supported data to choose one modality over another.³ Many have been used in combination, but even less data exist on combination efficacy. The authors suggest the following wart treatment options as those we feel should generally be attempted first (Table 47-2). We suggest that most common warts can be treated effectively, safely, and conveniently with liquid nitrogen cryosurgery or salicylic acid as first-line therapy and that combination treatments may be more efficacious than monotherapy, particularly in resistant cases.^{4,5} A table of alternative wart therapies not discussed is presented and should be used only by those with expertise in their application and adverse effect profile (Table 47-3).

TABLE 47-2 Primary Treatment Options

Anogenital warts

1. Cryotherapy
2. Podofilox
3. Imiquimod
4. Sinecatechins

Non-anogenital warts

1. Keratolytics (salicylic acid)
2. Cryotherapy (liquid nitrogen)
3. Cantharidin

TABLE 47-3 Alternative Treatment Options

Silver nitrate

Trichloroacetic acid

Levamisole

Topical zinc

Bichloroacetic acid

Interferon

Glutaraldehyde

Contact immunotherapy

Cidofovir

Formaldehyde

Localized heat therapy

Photodynamic therapy

Fluorouracil

Cimetidine

Laser

A. Keratolytic Therapy (Salicylic Acid). Salicylic acid is the most evidence supported of all wart therapies and tends to have a benign adverse effect profile—if anything usually mild local irritation and burning. It is often the first choice of dermatologist for common, periungual, subungual, and plantar warts. Recent meta-analysis of randomized control studies confirms

that salicylic acid has a definite, albeit modest, improvement over placebo.³ Salicylic acid exists in various concentrations (5% to 60%) and in different vehicles. It is also often combined with other therapeutic substances, many of which are available over the counter. Salicylic acid, along with other keratolytic agents, may act by mechanical removal of infected cells and wart virus and also by providing a mild inflammatory reaction that renders the virus more available to immunologic recognition and attack. These chemicals do not reach the basal layer where the HPV DNA is present. Duofilm and Occlusal (17% salicylic acid and 17% lactic acid in flexible collodion) are commercially available preparations; patients should be instructed to use them or other keratolytic paints properly (Table 47-4).

B. Cryotherapy. Although conclusive data over its efficacy have yet to be shown, seemingly stemming from the wide variation in clinical sites application modality, cryotherapy with liquid nitrogen has come into favor as a modality for treatment of all kinds of warts in nearly all locations. This technique carefully executed will remove the lesion and will usually leave no scar and little or no pigmentary change. Nonblistering therapy (10- to 20-second application) of liquid nitrogen with a cotton tip, melamine foam sponge, or spray canister every 2 to 4 weeks until resolution is generally effective. A 2-mm frost halo around the lesion suggests adequate application. Topical or injected local anesthesia prior to cryotherapy of large warts is reasonable. Better efficacy is most likely achieved with longer applications, yet this comes at the expense of increased side effects, such as pain, blistering, and scarring. This treatment destroys not the virus but the cells within and surrounding the lesion that contain HPV. Overzealous freezing should be avoided in pigmented individuals because of the risk of depigmentation. Caution should be exercised on periungual warts as damage to the nail matrix can lead to permanent damage. With respect to anogenital warts, cryotherapy may be used on both anal and urethral meatus warts, but

TABLE 47-4	Patient Instruction for Home Use of Keratolytics (Salicylic Acid and Lactic Acid)
<ul style="list-style-type: none">• Wash area thoroughly with soap and water.• Rub the surface of wart gently with a mild abrasive such as an emery board, pumice stone, or callus file. This is particularly important for plantar warts.• Apply keratolytic paint to the wart with a sharpened matchstick or toothpick.• Allow to dry.• Keep bottle tightly closed.• Repeat each night.• If area becomes red or tender, discontinue therapy until this subsides and then start again. Alternatively, keratolytic paint with a lower concentration of salicylic and lactic acids may be prescribed.• Do not apply paint to warts previously treated with liquid nitrogen until the inflammation has subsided.	

should be avoided with vaginal warts owing to the risk of vaginal perforation and fistula formation.²

- C. **Cantharidin.** Cantharidin (Cantharone), a mitochondrial poison derived from the blister beetle *Cantharis vesicatoria*, leads to changes in cell membranes, epidermal cell dyshesion, acantholysis, and blister formation. Cantharidin can be compounded with salicylic acid and podophyllin resin; occlusion for only 2 hours is needed with this combination. Thick hyperkeratotic lesions should be pared down before painting. The lesion should then be painted with cantharidin, allowed to dry, and covered with Blenderm or other nonporous occlusive tape; 40% salicylic acid plaster may be used to achieve greater activity. The tape is left on for 24 hours or until the area begins to hurt. A blister, often hemorrhagic, will form, break, crust, and fall off in 7 to 14 days; at this time, the lesion is pared down, and any wart remnants are retreated. Because the effect of cantharidin is entirely intraepidermal, no scarring ensues. Ring-like or “donut configuration” recurrences may be seen occasionally after treatment with cantharidin or, at times, following liquid nitrogen therapy. Owing to this agent’s toxicity, application by a physician is recommended. Verrusol, which contains 30% salicylic acid, 5% podophyllin, and 1% cantharidin, may be used in the same manner.
- D. **Podofilox.** Podophyllum resin (podophyllin), or podofilox, a cytotoxic agent that arrests mitosis in metaphase, is used primarily for the treatment of condyloma acuminata but may also be used on all other types of warts. The more commonly available preparation, podofilox 0.5% solution or gel (Condylox), should be applied twice a day for 3 days and then discontinued for 4 consecutive days. A cotton tip may be used for application with the solution while the gel may be applied with a finger. The same cycle is continued until eradication of the lesions or up to four cycles. The effectiveness as well as the irritant potential of this medication may be increased by covering with adhesive tape or plastic tape (Blenderm). Side effects include pain, burning, erosions, and itching. Weekly painting of the lesion with 10% to 25% podophyllum resin in compound tincture of benzoin is also an effective therapy, although it is now used rarely. Medication should be kept off uninvolved surrounding skin; this may be accomplished by applying a thin covering of petrolatum around the lesion before therapy. After the application dries, the area should be liberally powdered to prevent undue maceration and inadvertent transfer of podophyllin from the lesions to apposing normal skin. At the start of therapy, the medication should be left on for only 1 hour and then washed off, particularly in the vulvar area and the area under the foreskin. As therapy progresses, podophyllin should be left in place 4 to 6 hours before it is removed. Treated lesions may become inflamed and painful during the following 2 to 3 days. If the lesions are very verrucous or bulky, remove the mass of the wart first by curettage, and after healing, start podophyllin therapy. A topical anesthetic preparation is often useful during the period of pain. Podophyllin can cause severe irritation and, if absorbed in large quantities, may produce systemic toxic effects. It is inadvisable to apply it in large amounts to mucous membranes. Its safety in pregnancy has not been determined.²
- E. **Imiquimod.** Topical imiquimod (Aldara) 5% cream is an immune response modifier that has antiviral and antitumor activities. This drug is U.S. Food and Drug Administration (FDA) approved for genital warts, but may treat

other cutaneous warts as well. This drug activates dendritic cells and keratinocytes to produce interferon, tumor necrosis factor, and interleukin-12. The cytokine production promotes migration of Langerhans cells to lymph nodes, and virus-specific T cells are generated. A dramatic decrease in the quantity of HPV DNA and messenger ribonucleic acid occurs. The treatment regimen includes application to the wart and some surrounding skin three times a week for 6 to 10 hours, with subsequent washing with soap and water. Therapy should last a maximum of 16 weeks. Irritation and erythema are expected side effects and indicate an activation of the immune system; no systemic side effects have been observed. Induration, ulceration, vesicles, and hypopigmentation may also occur.

- F. Sinecatechins.** Sinecatechins (Veregen) 15% ointment is a newer drug composed of catechins extracted from green tea and used primarily for genital warts. Three times per day application by finger to affected areas should not exceed 16 weeks.² The thin layer of ointment to lesions does not need to be washed off. Side-effect profile is similar to imiquimod in that local irritation and erythema are expected. Burning, pain, pruritus, ulceration, and vesicular rash are other potential adverse effects.
- G. Tretinoin.** Tretinoin cream 0.05% has many applications in the realm of dermatology. With regard to treatment of warts, it appears to be most beneficial in the treatment of flat warts, with evidence to suggest it as first choice in the treatment of flat warts.⁶ Flat warts are often numerous and located on the face. As a mainstay in acne treatment, many dermatologists routinely prescribe tretinoin cream 0.05% and are comfortable with the side effects that are usually limited to local irritation. Tretinoin should be applied daily to warts in order to harness its affect through regulation of cell proliferation and differentiation.⁶
- H. Bleomycin.** Intralesional bleomycin, a cytotoxic drug that inhibits DNA synthesis, is effective for all varieties of recalcitrant warts. Various concentrations of the drug have been used, although the total dose must be carefully tracked over time to avoid potential systemic toxicity. Administration with a bifurcated needle and multiple punctures resulted in elimination of 92% of 258 treated warts.⁷ Local side effects that have been described are moderate-to-severe pain, nail dystrophy, and persistent Raynaud's phenomenon. The area needs to be anesthetized; full-strength bleomycin should be used; small amounts (0.025 to 0.1 mL/3 mm²) should be injected into the upper dermis, not exceeding a total of 1 mL per session. A dark hemorrhagic crust develops that should be pared after 3 weeks.
- I. *Candida* Antigen.** Injection of 0.1 mL of 1:1,000 *Candida* antigen into the base of each wart led to 85% clearance of common warts compared with 25% of controls. The *Candida* antigen is available from many pharmaceutical laboratories but is not approved by the FDA.
- J. Surgical Therapy.** Multiple surgical modalities are used in the treatment of warts, particularly in the management of large warts and multiple genital warts. Tangential excision with a sharp scissors or scalpel blade can be performed after application of local anesthetic. Aluminum chloride solution or electrocautery follow for hemostasis. Physical destruction with electrocautery is in itself a frequently used treatment modality; however, overzealous treatment may result in permanent damage through scarring. As such, care should be afforded to the depth of treatment.

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REFERENCES

1. Sri JC, Dubina MI, Kao GF, et al. Generalized verrucosis: a review of the associated diseases, evaluation, and treatments. *J Am Acad Dermatol.* 2012;66(2);292-311.
2. Workowski KA, Berman S. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep.* 2010;59:1-110.
3. Kwok CS, Gibbs S, Bennett C, et al. Topical treatments for cutaneous warts. *Cochrane Database Syst Rev.* 2012;(9):CD001781.
4. van Brederode RL, Engel ED. Combined cryotherapy/70% salicylic acid treatment for planar verrucae. *J Foot Ankle Surg.* 2001;40(1):36-41.
5. Housman TS, Jorizzo JL. Anecdotal reports of 3 cases illustrating a spectrum of resistant common warts treated with cryotherapy followed by topical imiquimod and salicylic acid. *J Am Acad Dermatol.* 2002;47(4 Suppl):S217-S220.
6. Micali G, Dall'Oglio F, Nasca MR, Tedeschi A. Management of cutaneous warts: an evidence-based approach. *Am J Clin Dermatol.* 2004;5:311-317.
7. Shelley WB, Shelley ED. Intralesional bleomycin sulfate therapy for warts. A novel bifurcated needle puncture technique. *Arch Dermatol.* 1991;127:234-236.

INTRODUCTION

Skin is uniquely available for diagnostic procedures as well as for the direct application of therapeutic agents. This ease of access allows multiple procedures to be performed in a short period with little discomfort to the patient. Most techniques are easily learned and require only simple equipment.

I. PUNCH BIOPSY The punch biopsy is an easily learned procedure that, in all but a very few circumstances, removes sufficient tissue for histopathologic study. The information derived from this procedure is important not only for diagnostic purposes but also to clarify a disease process and to assess the extent of tissue involved, because full-thickness tissue is usually obtained.

A. Procedure

- 1. Selecting Biopsy Site.** It is generally best to select a mature, well-developed, untreated lesion for biopsy. If vesicles or bullae are present, choose the earliest lesion available, and take care to keep the roof intact. The clinician should intentionally include adjacent normal skin. Several biopsies should be obtained from evolving eruptions or those with various types of lesions (in this instance, too, biopsy of early lesions may be of higher diagnostic yield). Lesions altered by trauma or prior treatment or “burned-out” areas will not yield useful information. It should be noted that biopsies on the legs and feet heal more slowly than proximal biopsies, especially if the circulation is poor. Therefore, if possible, choose a lesion above the knees. Choose a site entirely within the lesion. Avoid including normal skin in the biopsy unless specifically desired, in which case the pathologist should be informed of its inclusion and how the specimen is oriented.
- 2. Pre-anesthesia.** Clean the area gently with alcohol, taking care to leave scales, crusts, and vesicles intact. It is often useful to outline small lesions before the injection of local anesthetic, because the effect of epinephrine distorts and blanches the site.
- 3. Anesthesia.** Anesthetize the area by injecting into the deep dermis 0.2 to 0.5 mL of 0.5% to 2.0% lidocaine or 1% to 2% lidocaine with 1:100,000 epinephrine. Addition of sodium bicarbonate to the lidocaine (approximately one part of 8.4% sodium bicarbonate to nine parts of 2% lidocaine) will attenuate the burning sensation during infiltration. Patients allergic to local anesthetic ether compounds (procaine and tetracaine) can tolerate amide compounds (lidocaine and bupivacaine) without difficulty. For example, procaine (Novocaine) and lidocaine (Xylocaine) do not cross-react. Other alternatives for delivering local anesthesia include antihistamines such as diphenhydramine HCl or normal saline

with preservative. The local vasoconstriction produced by epinephrine will diminish bleeding and prolong the duration of anesthesia, thereby making the procedure easier to perform. For maximal vasoconstriction, a delay of 15 to 20 minutes post-injection is required. Epinephrine-containing solutions should be used with caution when vasoconstriction might interfere with the histopathologic findings (i.e., vascular lesions). Although some surgeons prefer to ring block an area with anesthesia, intradermal injection directly into or below a lesion appears to cause little or no perceptible microscopic alteration. Epinephrine-containing solutions are also used with caution when anesthetizing acral areas such as the penis, earlobes, and distal fingers or toes. However, more recent studies have indicated that there is likely no increased risk of ischemia or necrosis when using epinephrine-containing anesthetics in these areas, despite a history of circulatory disorders, thrombosis, diabetes, smoking, anticoagulation, or significant preoperative hypertension.¹ For larger excisions, patients with severe diabetic angiopathy, Raynaud disease, or those receiving monoamine oxidase inhibitors or β -blockers should not receive vasoconstrictors.

To minimize trauma for the patient, a 30- or 32-gauge needle should be used. The pain of needle insertion is reduced by reassurance, verbal distraction, quick placement, slow diffusion, and mechanical distraction, such as pinching or vibration immediately proximal to the injection site.² A topical anesthetic cream may be used to dull the pain of injection in children or for larger excisions. Topical anesthetics typically must be applied at least 1 hour before the procedure for maximal effects. Use of occlusion enhances the numbing effects. Using buffered anesthetic that is warmed to body temperature will help reduce the stinging sensation during injection.

4. **Instrument Choice.** Punch biopsy instruments have a cylindrical sharp cutting tip and a handle and are available in sizes ranging from 1 to 8 mm in diameter. The 4-mm punch is generally the most useful. About 6- to 8-mm punch biopsies tend to leave standing cone “dog ear” deformities at the edges, thereby needing subsequent wound repair. Removal of a specimen <4 mm in diameter may allow the histologic confirmation of a tumor, but is often inadequate for diagnosis of inflammatory processes.
5. **Punch Technique.** The skin surrounding the lesion should be stretched taut perpendicular to the wrinkle (relaxed skin tension) lines before the circular punch is inserted vertically, as demonstrated in Figure 48-1. When the punch is removed, an ellipsoidal defect will be left (Fig. 48-1, *insets*). The biopsy punch is pressed firmly downward into the lesion with a rotary cutting motion in one direction until it is well into the subcutaneous tissue (Fig. 48-1). If the incision is made only to mid-dermis, the tissue will be more difficult to remove and the wound will heal less rapidly and with a less satisfactory cosmetic result. Care should be taken to avoid underlying structures when visible (e.g., visible vessel, tendons), especially in areas with thinner skin.

The biopsied skin plug will either pop up or lie free within its circular margin. The specimen must be grasped gently and lifted out with a forceps without applying undue pressure. The base must be severed with a scissors or scalpel blade as deep into the fat as possible, and the tissue placed in 10% neutral

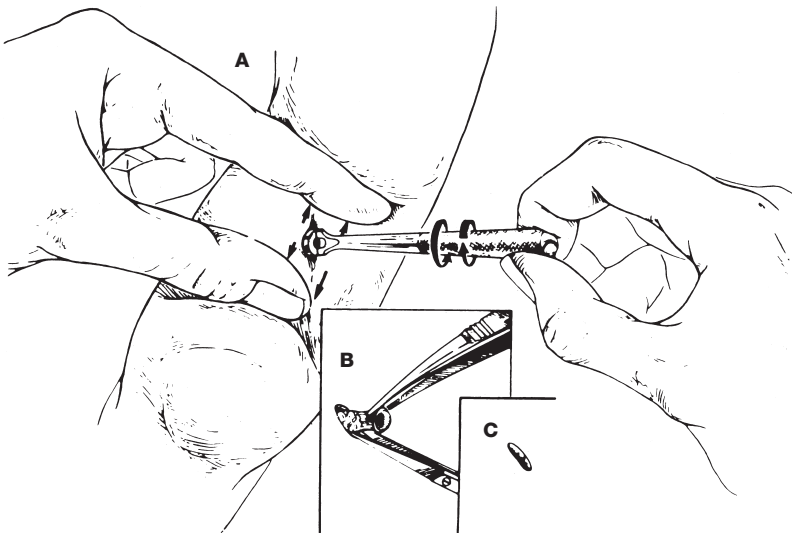


Figure 48-1. Punch biopsy technique. (A) Stretch the skin taut perpendicular to the relaxed skin tension lines before biopsy. (B) Gently grasp the skin plug with tissue forceps and sever as deep into the fat as possible. (C) An oval defect is left, which should be sutured.

buffered formalin. The amount of formalin should be at least 20 times that of the specimen by volume. To avoid an artificial split in the skin, grasp the specimen close to the base with the forceps.

Simple pressure is generally adequate for hemostasis. Rarely, 20% aluminum in ethyl alcohol (e.g., Drysol), ferric subsulfate (Monsel solution), absorbable gelatin (Gel foam), or electrodesiccation may be needed. Ferric subsulfate may occasionally result in pigmented tattoos and may destroy more tissue than other methods. Lesions heal more rapidly and with a linear scar if they are closed with appropriate sutures and not left as a round defect (sutures are left for 5 to 7 days on the face or 10 to 14 days on the trunk). Adhesive strips may also be applied across the defect (left for 14 to 21 days). If the patient cannot return for suture removal, an absorbable suture can be used to close the punch biopsy site.

The histologic interpretation of cutaneous reaction patterns requires a great deal of judgment and experience. It is wise to seek the help of a dermatopathologist. A clinical pathologic correlation should be made and follow-up consultation or a second opinion requested if there are questions regarding the diagnosis, especially of a pigmented lesion.

II. SHAVE BIOPSY A shave biopsy allows the easy removal of epidermal and papillary dermal tissue for histopathologic inspection. It removes that portion of skin elevated above the plane of surrounding tissue and is useful for biopsying or removing many exophytic benign epidermal growths, including keratoses and viral tumors. Shave biopsies are most useful for obtaining

a tissue diagnosis of malignant lesions such as basal cell and squamous cell carcinomas. This procedure is quickly and easily performed, heals rapidly, and yields a good cosmetic result. In addition, it leaves the lower levels of the dermis intact if further procedures such as curettage, electrosurgery, and cryosurgery are necessary. The decision to perform a shave biopsy requires some judgment and, in particular, a reasonably good impression of the preoperative diagnosis. A shave biopsy may fail to distinguish, for example, between an actinic keratosis and an invasive squamous cell carcinoma if the shave is too superficial. It is controversial to perform a shave biopsy for melanoma diagnosis since it may fail to obtain the entire depth of lesion. Finally, this technique typically is not preferred for diagnosing inflammatory lesions.

A. Pre-biopsy Preparation. Clean and anesthetize the area as noted above for punch biopsy.

B. If a Substantial Margin of Tissue Surrounding and Below the Lesion Is Needed, the shave should take place immediately after injection of anesthesia, when the tissue is still elevated from the injection fluid (Fig. 48-2, inset, right). Tissue can be removed with either a no. 15 scalpel, a halved Gillette Super Blue Blade or Personna Blade, or a Personna DermaBlade (Fig. 48-3). The last two blades have the potential advantages of being thinner, sharper, and more flexible. When handheld, they can be used flat or bent between two fingers to the precise arc desired to conform to the shape of the lesion and the depth of the biopsy (Fig. 48-2). If the elevated lesion alone is being removed, wait a few minutes until any edema secondary to anesthetic subsides. It is also often helpful to use the fingers of the nondominant hand to create some counter tension near the biopsy site or to have a pair of forceps to help stabilize and remove the biopsied tissue. As with punch biopsies, the specimen may be put into formalin and submitted for pathologic examination.

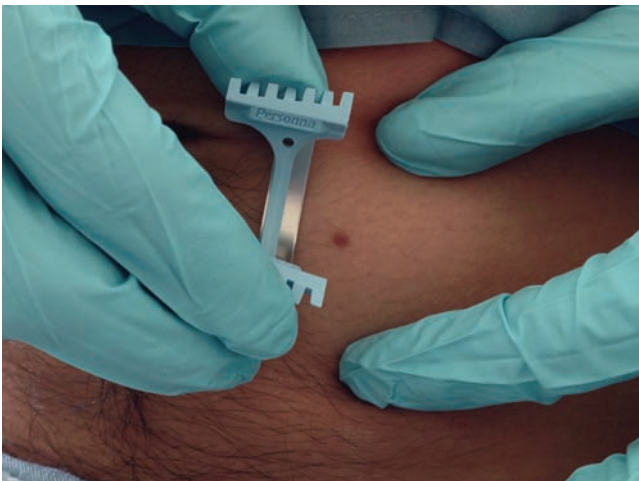


Figure 48-2. Shave biopsy technique.



Figure 48-3. Various tools available to perform a shave biopsy.

- a. When trying to obtain tissue from the upper to mid-dermis, a saucerization technique can be used. Although this procedure requires even greater clinical judgment and technical expertise, it is useful when deeper lesions are present or when having more tissue present can be helpful for making a diagnosis. For example, when biopsying a suspicious superficial pigmented lesion, a Gillette or Personna blade can be bent into more of a U-shape and used in a scooping motion to perform the saucerization biopsy.
- b. Pedunculated lesions may be easily removed by the use of scissor biopsy or even with a flat shave biopsy.

C. Pressure, Ferric Sub sulfate (Monsel's Solution), 20% Aluminum Chloride in Ethyl Alcohol, or Electrodesiccation may be used for hemostasis. Ferric subsulfate is best avoided on the face as it can lead to dyspigmentation.

III. EXCISIONAL BIOPSY An excisional biopsy should be considered when (i) there are lesions with active expanding borders; (ii) the junction of lesion and normal skin is important to survey; (iii) the lesions are atrophic, sclerotic, or bullous; (iv) it is important to acquire adequate full-thickness skin, for example, in panniculitis such as erythema nodosum; and (v) the lesion may be melanoma.

IV. CURETTAGE Curettage is a useful technique for removing both benign and malignant cutaneous lesions. Commonly removed benign growths include warts, molluscum, milia, and keratoses. When combined with electrodesiccation, it is also effective for treating various basal and squamous cell carcinomas. Curettage before wide local or Mohs' micrographic excision may allow the surgeon to debulk and define the margins of the tumor.

The curette, a cutting instrument with a circular or oval, loop-shaped cutting edge and a handle, is available in varying sizes. Large curettes will remove masses of tissue rapidly, whereas smaller ones are useful to probe for small extensions of lesions into subjacent dermis. The 4-mm-diameter curette is the most used size. The more friable the tissue, the easier it is to curette. Curettage is difficult to perform on normal skin. The curette is neither sharp enough nor does it have sufficient strength for this purpose. The resulting tissue is usually too fragmented and distorted for pathologic examination.

A. Procedure

1. Clean the area with alcohol.
2. Anesthesia is not always necessary. The process of anesthetizing can be more painful than the surgical procedure itself when removing lesions such as seborrheic keratoses, molluscum, and milia. If anesthesia is used, wait until any swelling has diminished or subsided, because it is difficult to scrape the spongy tissue.
3. Apply the cutting edge of the curette to the lesion and remove the tissue with a firm, quick, downward scoop (Fig. 48-4). The first tissue removed will come off relatively intact and should be submitted for pathologic examination if indicated. Scrape the base and margins of the lesion well. Normal dermis is resilient and feels rough and scratchy when scraped, whereas diseased skin has softer composition.

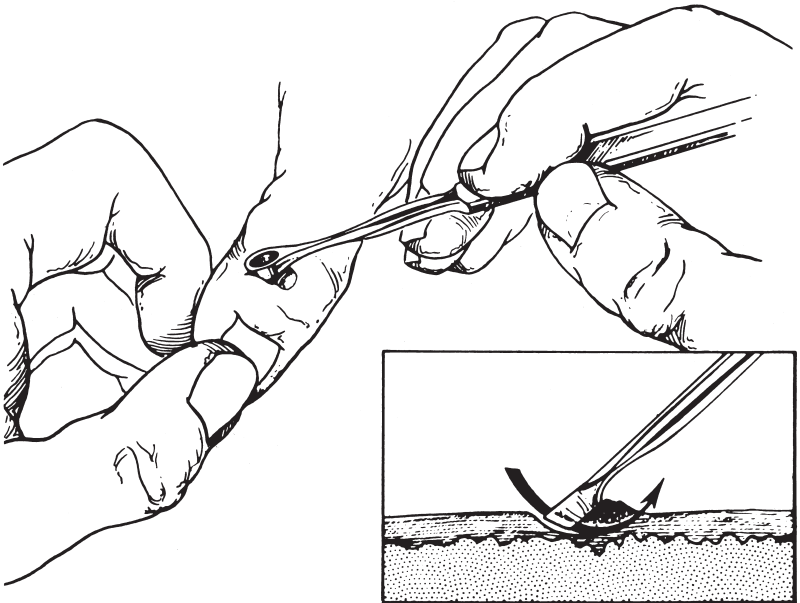


Figure 48-4. Curettage technique.

4. Hemostasis is secured by pressure, hemostatic agents [ferric subsulfate (Monse's solution), 20% aluminum chloride in ethyl alcohol (Drysol)], or electrodesiccation. Use of pressure alone yields the best cosmetic result.

V. ELECTROSURGERY These small electrosurgical units found most often in physicians' offices and hospital clinics are versatile, useful tools. They deliver a high-frequency alternating current, producing an electrical field about the tip of the treatment electrode. The high resistance of tissue to this electric current generates heat. The electrode tip delivers the current but does not become hot.

The principal uses of electrosurgery are (i) the destruction of benign superficial lesions such as warts, keratoses, and skin tags; (ii) hemostasis and the ablation of vascular growths; and (iii) the destruction of some malignant tumors of the skin. Special precautions should be taken when using these instruments on patients with indwelling cardiac pacemakers (especially the spontaneous, demand type) or implanted cardiac defibrillators. Electrocautery is often the best choice for these patients. There is considerable risk of spread of hepatitis B or other viral-associated infections such as acquired immunodeficiency syndrome from patient to patient with the use of reusable, nonsterilized electrosurgical electrode tips. Transmission of hepatitis B virus by such electrodes has been demonstrated during simulated use with electrodesiccation and has been documented with reusable needles such as those for ear piercing, tattoo procedures, or acupuncture.³ Sterile disposable needle electrodes should be used for the procedure. If only reusable needle electrodes are available, gas or steam sterilization is recommended after each use.

The various types of electrosurgery include electrodesiccation, electrofulguration, electrocoagulation, electrosection, and electrocautery. Electrodesiccation and electrofulguration produce superficial destruction by dehydrating cells. Both types of electrosurgery are monoterminal, markedly damped, high-voltage (2,000 V or more), low-amperage (100 to 1,000 mA) operations where the patient is not incorporated into the circuit. The needle is either held in contact with the tissue (electrodesiccation) or kept a short distance away (electrofulguration), and the current is transmitted through a spark. The tissue is dehydrated by the heat produced by tissue resistance to the electric current.

Electrocoagulation produces deeper, more severe destruction, primarily by heat and secondarily by disruptive mechanical forces. This operation is a biterminal, relatively low-voltage (under 200 V), low-frequency, high-amperage (2,500 to 4,000 mA) procedure in which the patient is grounded by being placed in contact with a large "indifferent" electrode. The treatment needle, placed in or on the tissue, delivers an intensely hot current and literally "boils" and coagulates the lesion. Electrocoagulation is used primarily for large lesions that require extensive destruction, some neoplasms, or highly vascular tumors such as pyogenic granulomas. It produces wider and deeper damage, more scarring, and better hemostasis. Vigorous electrocoagulation may produce delayed hemorrhage.

Electrosection causes minimal lateral heat spread and tissue damage and has the added advantage of simultaneously achieving hemostasis and cutting. This operation is done through a biterminal, slightly damped, low-voltage, and high-amperage current. It is most useful for large, bulky lesions that are allowed to heal by secondary intention, such as acne keloidalis nuchae and rhinophyma.

Electrocautery uses a red-hot wire heated by a low-voltage (5 V), high-amperage (15 A) current produced by a step-down transformer with a variable reactor. In this instance, the wire itself is hot. It is not an electrode, and no current flows into the patient. Disposable battery-operated units are available in high- and low-temperature varieties. Electrocautery is an excellent alternative when hemostasis is required in patients with indwelling cardiac pacemakers or defibrillators. The extent of tissue destruction of lesions is readily apparent and sharply localized about the cautery tip.

A. Procedure

1. Clean the skin with alcohol and let dry. Alcohol and some anesthetic gases are flammable. Strict asepsis is unnecessary because the procedure is itself antiseptic.
2. Infiltrate with lidocaine-containing epinephrine. Treatment of some lesions, such as telangiectatic vessels, is so rapid that anesthesia is not required.
3. When tissue is needed for histologic examination, first curette the lesion, removing all the accessible pathologic tissue. The difference in texture between abnormal and normal tissue becomes difficult to “feel” after a lesion has been altered by electrosurgery. Continue the curettage until the base and borders of the lesion are firm and clean and all pockets of abnormal material have been scraped away. If there is a diagnostic question, shave excision is a better method for obtaining intact tissue specimens for histologic study. It may be followed by curettage and electrosurgery or by electrosurgery alone.
4. Apply the electrodesiccating current onto or into the tissue and deliver recurrent bursts of electricity (Fig. 48-5). It is not necessary to deliver a large spark, because this chars tissue, leads to greater tissue destruction, and offers no added therapeutic advantage. The area being treated should be as dry as possible.

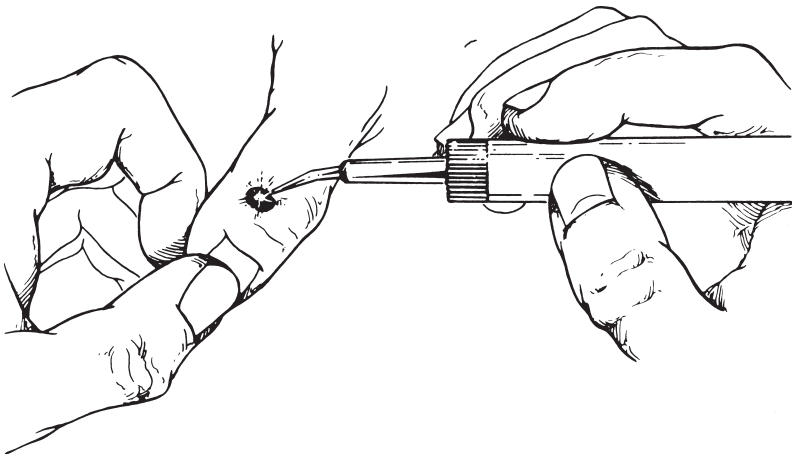


Figure 48-5. Electrosurgery technique.

- a. Use as little current as needed when treating spider and other angiomas and seborrheic keratosis, or when ensuring hemostasis at the base of a lesion.
 - b. Warts, actinic keratoses, molluscum contagiosum, and skin tags should be treated with slightly more current. The best technique for treating warts is to insert the needle electrode into the lesion and deliver current until the lesion “bubbles.” The gelatinous charred tissue is removed with a curette, and a spark of less intensity is used to desiccate the base lightly. Deeper destruction will not increase the cure rate and will result in a more prolonged healing time and excessive scarring. Inserting a 30-gauge needle (attached to a plastic syringe) into the lesion and then touching the active electrode to the needle shaft allows more precise destruction.
 - c. Repeated cycles of curettage and electrodesiccation are needed when removing malignant cutaneous neoplasms.
5. The wound produced by electrosurgery is best treated with petrolatum or antibiotic ointment and a nonadherent dressing. Reepithelialization takes place from the base and sides of the lesion and is complete in 1 to 6 weeks, depending on the size of the lesion, its location, and the amount and depth of tissue destruction.

VI. CRYOSURGERY The application of cold to the skin treats a wide spectrum of skin conditions, including preneoplastic and neoplastic processes. Cryosurgery also treats benign growths such as seborrheic keratoses, viral warts, lentigines, keloids, and myxoid cysts. Cryogenic agents are easy to apply, usually require no anesthesia, and cause epidermal–dermal separation above the basement membrane, thereby leaving no scarring after reepithelialization. The lower the boiling point of the agent, the more efficient its freezing capabilities. The boiling point of Freon 11 is $+23.8^{\circ}\text{C}$; that of ethyl chloride, $+13.1^{\circ}\text{C}$; that of Freon 114, $+3.6^{\circ}\text{C}$; that of dichlorotetrafluoroethane (Frigiderm), $+3.6^{\circ}\text{C}$; that of Freon 12, -29.8°C ; that of solid CO_2 , -78.5°C ; that of liquid nitrous oxide, -89.5°C ; and that of liquid nitrogen, -195.6°C . Liquid nitrogen, which is readily available from medical and industrial sources, is inexpensive, noncombustible, and has become the standard therapeutic agent.

Skin is relatively resistant to freezing because of its rich vascular supply and because frozen tissue itself acts as a good insulator. Although skin freezes at 0°C to -2°C , it is necessary to cool the tissue to -18°C to -30°C for destruction to occur. Application of liquid nitrogen to the skin with a cotton-tipped applicator stick four times within 60 seconds will lower the temperature 2 mm below the cutaneous surface to -18°C . Direct spray of liquid nitrogen for an equal period will cool the tissue to -90°C and, after 120 seconds, to -125°C at 2 mm and -70°C at 5 mm below the skin's surface. Such temperatures are needed only for cryosurgery of skin cancer. The degree of injury is roughly proportional to the intensity of freezing. Repeated freezing and thawing is more damaging than a single freeze. Rapid cooling and slow thawing produce the most damage.

With cryosurgery, multiple tissue effects occur. Although the exact mechanism of injury is unclear, all of the following take place in frozen tissue: (i) mechanical damage to cells by intracellular and extracellular ice formation;

(ii) osmotic changes related to dehydration of cells and increased concentration of electrolytes as a result of water withdrawal during ice crystal formation; (iii) thermal shock, a term used to denote a precipitous fall in the temperature of living cells to subnormal temperatures above 0°C; (iv) denaturation of lipid-protein complexes within the cell membrane; and (v) vascular stasis due to freezing of feeding vessels with resulting necrosis of tissue.

Side effects of cryosurgery include short- and long-term discomfort and pigmentary changes. Freezing with liquid nitrogen is accompanied by a stinging, burning pain that peaks during thawing, approximately 2 minutes after treatment is over. It is usually unnecessary to use local anesthesia. Pressure, which increases both the rate and depth of freezing, should be applied only to lesions over thick, hyperkeratotic sites such as the feet. Freezing of lesions on the hands, feet, lips, ears, and eyelids is more painful than elsewhere. Within minutes of thawing, a triple response with redness, wheal, and surrounding flare will develop. Intense edema or a blister at the dermoepidermal junction forms 3 to 6 hours later, flattens in 2 to 3 days, and sloughs off in 2 to 4 weeks. Reepithelialization is under way within 72 hours of superficial freezing, and superinfection is rare.

Cryosurgery may also produce long-term nerve damage. Extra care must be taken when treating areas in which nerves lie superficially (e.g., the sides of the fingers). Because the nerve sheath is relatively resistant to cold injury, sensory loss is almost always temporary, though a year or more may pass before full recovery of normal sensation.

Pigment alteration occurs since melanocytes are more susceptible than keratinocytes to cold. Melanocytes begin to die in the range of -3°C to -14°C. As a result, mild hypopigmentation is sometimes seen in areas previously frozen with liquid nitrogen. The physician should be especially mindful of this principle when treating patients with darker skin, where hypopigmentation may be more cosmetically unacceptable.

A. Procedure

1. Liquid nitrogen is best kept in specially constructed vacuum flasks. It may be poured into an insulated styrofoam cup or spray apparatus for immediate use. Liquid nitrogen can rarely cause normal thermos bottles to explode, and an air vent must always be present in all storage apparatus.
2. When using the application tip method, dip a loosely wrapped cotton-tipped applicator into the nitrogen and place it promptly onto the cutaneous lesion (Fig. 48-6). Large fluffy swabs such as those used for sigmoidoscopy or gynecologic examination will hold greater amounts of nitrogen. When these are used, the cotton tip should be shaped into a point slightly smaller than the lesion under treatment. Do not apply pressure routinely. Thick lesions should be surgically pared first and may be treated with moderate pressure. Small lesions are treated most successfully by interrupting contact between the applicator and skin frequently, preventing the zone of freezing from extending to a greater depth and width than necessary. Rolling the applicator over the surface can treat large lesions.
3. A 5- to 30-second application is adequate for small, superficial lesions, such as lentigines, especially when located on thin skin. Most other benign growths, such as warts, keratoses, and molluscum contagiosum, require a 10- to 60-second application. Within seconds, the lesion

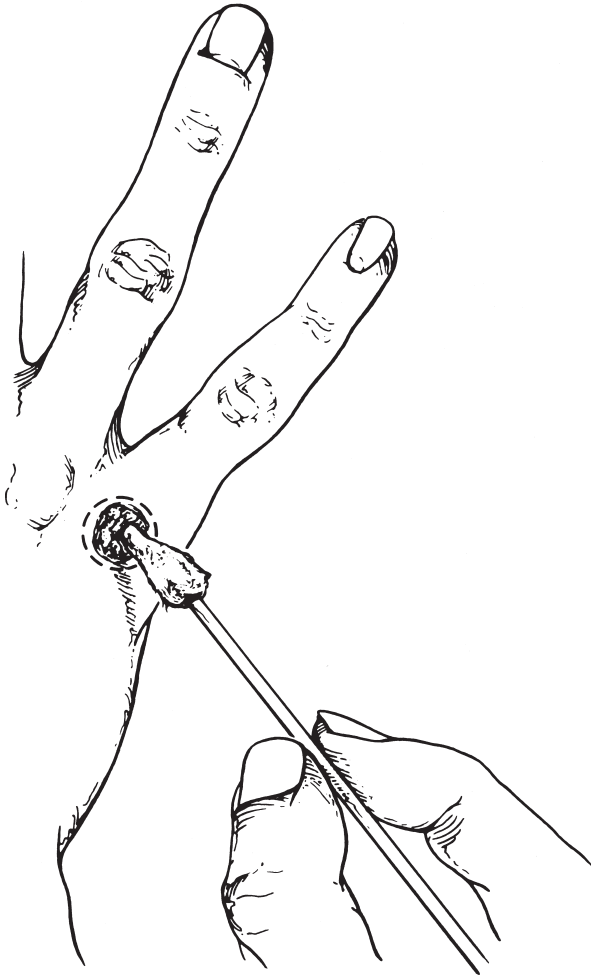


Figure 48-6. Cryosurgical technique. Liquid nitrogen is delivered to the lesion on a loosely wrapped cotton-tipped applicator stick (or larger cotton swab). The nitrogen should be repeatedly applied until the freezing front extends 1 to 3 mm around the lesion (*dotted line*).

begins to turn white. Nitrogen is applied repeatedly until the white freezing front extends 1 to 3 mm onto the surrounding normal skin (Fig. 48-6). The zone of frozen tissue reaches a depth of 1.5 to 2.0 mm within 1 minute of the initiation of nitrogen application and does not advance significantly. If utilizing a spray technique, apply the liquid nitrogen for shorter pulses since freezing occurs more rapidly and at greater depth.

4. The posttreatment lesion usually requires no dressings. If a topical anesthetic cream such as 4% to 5% lidocaine is applied to lesions in the immediate posttreatment period, pain will be sharply diminished. If a blister forms, it may be large or hemorrhagic. If it is uncomfortable or awkward, it may be decompressed with a sterile blade or pin, leaving the roof intact. Patients with warts should be seen in 2 to 4 weeks, at which time the lesions are debrided and any remaining wart tissue is either refrozen or treated with caustics or electrodesiccation.

REFERENCES

1. Firoz B, Davis N, Goldberg LH. Local anesthesia using buffered 0.5% lidocaine with 1:200,000 epinephrine for tumors of the digits treated with Mohs micrographic surgery. *J Am Acad Dermatol*. 2009;61(4):639-643.
2. Arndt KA, Burton C, Noe JM. Minimizing the pain of local anesthesia. *Plast Reconstr Surg*. 1983;72(5):676-679.
3. Sheretz EF, Davis GL, Rice RW, et al. Transfer of hepatitis B virus by contaminated reusable needle electrodes after electrodesiccation in simulated use. *J Am Acad Dermatol*. 1986;15(6):1242-1246.

CYTOLOGIC SMEARS

I. BACKGROUND Cytologic techniques in dermatology are useful in the diagnosis of bullous diseases, vesicular viral eruptions, and molluscum contagiosum. Other diseases that are also amenable to diagnosis by cytology include some genodermatoses such as Hailey-Hailey and Darier; drug hypersensitivity such as toxic epidermal necrolysis (TEN); infections such as staphylococcal scalded skin syndrome (SSSS) and leishmaniasis; and even tumors such as basal cell carcinoma (BCC), mastocytoma, and squamous cell carcinoma. However, these techniques require more experience in their interpretation. The cytologic smear technique allows for rapid confirmation of a suspected diagnosis while awaiting histopathologic processing and interpretation of biopsies.

II. TECHNIQUE

- A. Select an Early Lesion** that shows no signs of trauma or infection.
- B. Separate or Remove the Blister Top** with a scalpel or sharp scissors. Absorb excess fluid with a gauze pad.
- C. Gently Remove the Blister Contents** and scrape the floor and edges of the vesicle with a no. 10 or 15 scalpel blade or curette.
- D. Make a Thin Smear** on a clean glass slide. With solid lesions such as molluscum, squeeze the material between two slides.
- E. Air-Dry.** If the following reagents are available, fix tissue by dipping it four to five times in 95% ethanol or methanol or immerse the slide in these solutions for 1 to 2 minutes.
- F. Stain** with Wright, Giemsa (one-half dilution with tap water for 30 to 40 seconds), or hematoxylin and eosin stain. Ideally, 20- to 25-minute incubation is preferable for Wright stain.
- G. Microscopic Appearance.** Examine first with a low-power objective to gain an impression of cell size and depth of stain relationships, then examine with 45 \times or oil objective for the morphologic details.
 - 1. Herpetic Viral Infections.** The Tzanck smear demonstrates multinucleated giant cells with nuclear molding, occasional nuclear inclusions, blurred chromatin ("ballooning degeneration"), and occasional atypical-appearing mononucleate cells (Fig. 49-1). These giant cells represent infected keratinocytes. Without direct immunofluorescent antibody staining, it is impossible to differentiate between herpes simplex virus and varicella-zoster virus. Between 60% and 70% of Tzanck smears show the characteristic changes of herpesvirus infection. Occasionally, intranuclear inclusion bodies may be identified.

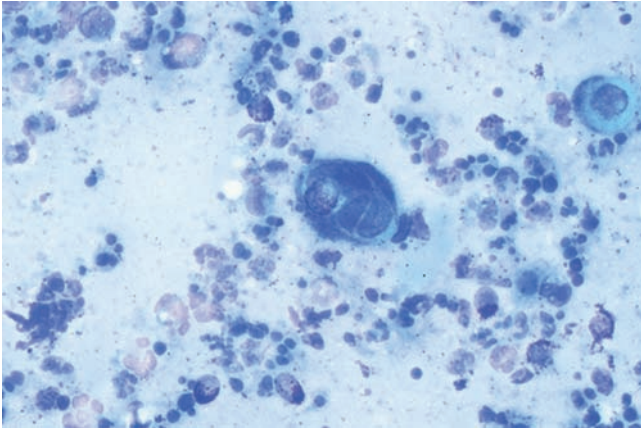


Figure 49-1. Positive Tzanck smear in viral herpetic infection. Multinucleated giant cells, with atypical-appearing mononucleate cells, as well as normal keratinocytes and inflammatory infiltrate primarily consisting of neutrophils. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

2. **Molluscum Contagiosum.** Henderson-Patterson inclusion bodies (virus-transformed keratinocytes) appear as multiple, large, oval to round, smooth-bordered basophilic masses up to 25 μm in diameter.
3. **In Some Bullous Eruptions, Acantholytic Rounded Keratinocytes Are Seen** in the cytologic smear. When determining between SSSS and TEN, the presence of necrotic keratinocytes and inflammatory cells points toward a diagnosis of TEN.
4. **In BCC, Tzanck Smear Shows Clustered Basaloid Cells**, often with peripheral palisading.

FUNGAL SCRAPING AND CULTURE

I. BACKGROUND Two techniques are available for diagnostic confirmation of a fungal infection: direct microscopy and fungal cultures. Immediate confirmation of the presence of a fungal infection may be accomplished easily by microscopic identification of organisms. Fungal culture will identify the causative organism specifically. This is therapeutically important because some nondermatophytic molds such as *Scytalidium hyalinum* as well as *Candida* species may mimic dermatophytes on potassium hydroxide (KOH) examination but are often resistant to conventional dermatophyte therapy.

II. TECHNIQUE All scaling lesions from the scalp, angles of the mouth, axillae, groin, inframammary area, and feet, as well as blisters on the hands and feet, should be considered for both fungal scraping and fungal culture.

A. Scraping Examination

1. Skin

1. If lesions are soiled or macerated, clean the skin well with alcohol and let dry.
2. Scrape with a scalpel or edge of a microscope slide at the active border of a lesion and collect scales on a glass slide. With blistering eruptions, the fungus is in the roof of the vesicle, which can be either gently dissected off with sharp scissors or scalpel or reflected back and the underside scraped with a no. 15 scalpel blade.
3. When obtaining culture specimens from anxious or uncooperative patients, vigorous rubbing of the lesion with a moistened sterile cotton swab provides an effective atraumatic alternative to actual scraping.¹
4. Small, thin fragments of tissue may be examined directly. Large pieces should be minced with a scalpel blade. Thick pieces should be discarded.
5. Gather scrapings together in the center of the slide.
6. Mix with one to two drops of 10% to 20% KOH. Add a coverslip and heat gently, but not to boiling, for 15 seconds. Note that two types of KOH are available: one in water and the other in dimethyl sulfoxide (DMSO). The KOH in DMSO does not require heating. An alternative preparation is covering the scrapings with either chlorazol black E stain or Swartz-Lamkins stain, which stain fungal hyphae, providing a contrast between fungi and background cells (Fig. 49-2).
7. Let KOH slides cool for 10 minutes (during which time the tissue is hydrolyzed and rendered clear) and then press the coverslip gently to flatten the tissue and push out air bubbles.
8. Examine under a scanning lens or high-dry magnification. It is very important to avoid getting KOH on the microscope objective, as it will etch the lens. The diaphragm should be closed down and the condenser lowered as far as possible. The ease of identification of hyphae varies inversely with the intensity of light passing through the slide.
9. In KOH preparations, hyphae and spores will appear as refractile tubes and oval bodies against the background of cells and debris. It is not possible to make a species identification from tissue scrapings.

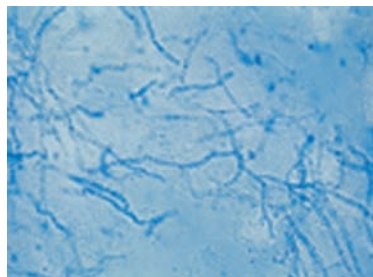


Figure 49-2. Fungal scrapings using the Swartz-Lamkins stain.

Using Swartz-Lamkins stain, hyphae and spores appear blue against the unstained background of cells. This fungal stain consists of a dye, a surfactant to clear the tissues quickly, and less KOH (2%) content to avoid damaging microscope lenses. Chlorazol black preparations will stain hyphae green against a cellular background. Because the hyphae stain selectively and are seen more easily with these stains, slides may be scanned more quickly at a lower power.²

2. Hair and Nails

1. Examine the scalp with a Wood's lamp. If individual lesions fluoresce, pull out 10 to 15 hairs for examination. Otherwise, examine scales and 10 to 15 randomly plucked hairs from the involved site. Fungus invades the hair in two ways: ectothrix involvement, where the hair shaft is surrounded by tiny spores, and endothrix infection, where the spores are found inside the hair shaft. Ectothrix fungi include *Microsporum* species as well as *Trichophyton mentagrophytes* and *Trichophyton verrucosum*. Endothrix infections are seen with *Trichophyton tonsurans*, *Trichophyton violaceum*, and *Trichophyton schoenleinii*. Altered, dystrophic, hypertrophic, or pigmented nails should be snipped off and minced on a slide.³ Subungual debris is less suitable for direct examination, though it is preferable for fungal culture.
2. Heat the specimen on a slide or in a test tube with 10% to 40% KOH and let cool for 15 to 30 minutes. Tissue may then be stained or examined directly.

B. Culture. In addition to direct examination of scales, scrapings from a suspicious lesion should be cultured at room temperature on Sabouraud glucose agar, Sabouraud agar with chloramphenicol and cycloheximide (Mycobiotic, Mycosel), or dermatophyte test medium (DTM).

Sabouraud agar with chloramphenicol and cycloheximide is more selective for dermatophytes because the chloramphenicol and cycloheximide inhibit bacteria and other contaminants. DTM contains cycloheximide, gentamicin, and chlortetracycline, preventing the growth of bacteria and saprophytic fungi. DTM contains phenol red, which turns the agar from yellow to bright red when its pH becomes alkaline from dermatophyte growth. Contaminant growth does not alter the pH of the medium. Using DTM medium, the specimen should be inoculated onto the media and the cap loosely placed, thereby providing the fungi with the air they require for growth. If no color change takes place within 2 weeks, the culture may be discarded. If the color does change, it may be presumed that a pathogenic dermatophyte or yeast is present. Microscopic examination of the culture (culture mount) should then identify the exact species.

WOOD'S LAMP EXAMINATION

I. BACKGROUND Invented in 1903 by Robert W. Wood, Wood's lamp uses a light source with a glass filter containing barium silicate and 9% nickel oxide to emit bands of light between 320 and 400 nm (peak 365 nm). The light source may be from a fluorescent tube, a mercury vapor lamp, a light-emitting diode, or an incandescent light. Tissue fluorescence occurs when Wood's light is absorbed and visible light is emitted; however, this is minimal in normal skin due to the presence of amino acids, elastin, and melanin. Fluorescent bulbs

(black lights) emitting a similar, although slightly broader, spectrum light are also available.

II. TECHNIQUE Initially used for the detection of fungal infection, Wood’s lamp examination may also be useful in clinical settings where bacterial infection, pigmentary disorders, porphyria, tetracycline use, or exposure to fluorescent materials is suspected (Tables 49-1 and 49-2).

A. Detection of Scalp Tinea. Hairs infected with *Microsporum audouinii*, *Microsporum canis*, or *Microsporum distortum* fluoresce bright blue-green under Wood’s lamp. Fluorescent hairs may then be selected for microscopic examination and culture. Unfortunately, the emergence of *T. tonsurans*, a nonfluorescent dermatophyte, as the most common cause of tinea capitis limits the usefulness of screening with Wood’s lamp examination.

B. Detection of Other Fungal Infections. While often clinically imperceptible, tinea versicolor fluoresces golden yellow. Wood’s light examination will allow the accompanying pigmentary changes to be seen more vividly.

C. Detection of Bacterial Infections

- 1. Erythrasma, an intertriginous infection caused by *Corynebacterium minutissimum*, fluoresces brilliant coral red or pink-orange. The fluorescent substance is a water-soluble porphyrin that may be washed off the skin causing a falsely negative Wood’s lamp examination.
- 2. *Pseudomonas aeruginosa* infections produce a yellow-green fluorescence due to pyocyanin. Its fluorescence is detectable before obvious purulence appears. Therefore, Wood’s lamp examination is a useful screening tool for infections in burn patients.

TABLE 49-1	Proper Technique of Wood’s Lamp
Warm up lamp for approximately 1 min	
Cleanse skin (unless erythrasma is suspected)	
Make examination room completely dark	
Position lamp 4–5" from skin	

TABLE 49-2	Diagnostic Uses of Wood’s Lamp
Scalp tinea	
Other fungal disease	
Bacterial infection (erythrasma, <i>Pseudomonas</i>)	
Pigmentary disorders	
Porphyrins	
Some drugs	
Other (fluorescent ingredients or markers)	

D. Delineation of Pigmentary Disorders. Epidermal melanin prevents transmission of Wood's light past the epidermis in normal skin. Therefore, variations in epidermal pigmentation (freckles, melasma, and vitiligo) are more apparent under Wood's lamp while variations in dermal pigmentation (Mongolian spot, some instances of postinflammatory hyperpigmentation) are less apparent or unchanged as compared with ambient light.

If transmitted to the dermis, Wood's light will cause dermal collagen to fluoresce white to blue. Thus, Wood's light can distinguish hypopigmented from amelanotic areas. Amelanotic areas will have true white to blue fluorescence since there is no epidermal melanin to interfere with Wood's light transmission. Wood's lamp can be used to examine patients with vitiligo, albinism, leprosy, and other disorders of hypopigmentation and to screen newborns for the small, ash-leaf-shaped, white macules indicative of tuberous sclerosis.

E. Detection of Porphyrins. Acidified urine, feces, and, rarely, blister fluid from patients with porphyria cutanea tarda will fluoresce brilliant pink-orange.

F. Drug Detection. Patients who ingested tetracycline during childhood may have teeth that fluoresce yellow. Topical tetracycline therapy will cause treated sites to fluoresce yellow, while oral tetracycline therapy may cause pink fluorescence of the nail bed lunulae.

G. Miscellaneous. Fluorescent ingredients or markers in cosmetics, medications, or industrial compounds may be detected with Wood's lamp examination.

PATCH TESTING

I. BACKGROUND Patch testing is a diagnostic test used to validate a clinical diagnosis of allergic contact sensitization; it may identify one or more causative agents. Additional applications include screening-specific patients with chronic or unexplained eczematous eruptions (e.g., hand and foot dermatoses). It is a unique method for reproducing disease in diminutive proportions, relying on the fact that sensitization affects the whole body and may therefore be elicited at any cutaneous site (i.e., the primary mechanism being type IV delayed hypersensitivity). The patch test is easier and safer than a "use test" because test items can be applied in low concentrations on small areas of skin for short time durations, although use tests are helpful for determining relevance of certain allergens and identifying personal care products that should be avoided.

II. TECHNIQUE Patch testing is performed on normal hairless skin of the back or inner arms. It is important to delay patch testing until any acute inflammation has subsided in areas of patch test application. Re-exposure to the culprit antigen may cause disease exacerbation and if the causative allergen is placed on the skin for patch testing purposes, patients may develop a so-called recall reaction of their dermatitis. Antihistamines will not influence the results. However, systemic steroids and/or aggressive topical steroid application to the patch test site within 1 to 2 weeks of patch testing may cause false-negative results. For optimal patch test results, it is recommended that

systemic steroids and other systemic immunosuppressives be discontinued 2 to 4 weeks, respectively, before patch tests. If patients cannot discontinue systemic steroids, then they should be tapered to as low a dose as possible before patch testing. However, false negatives may occur.

Test only with potential allergens. There are no methods available for assaying primary irritants easily. Ideally, the substances being tested should not irritate the skin. The resulting irritant dermatitis may be misinterpreted as an allergic contact dermatitis—a false-positive result. Cosmetics may be applied full strength, but items of unknown irritant potential should be diluted to 1% to 2% in petrolatum, mineral oil, or less preferably, water. Suitable dilution and vehicle data are available in Fisher's *Contact Dermatitis*⁴ and other references cited at the end of this chapter.

The most widely used initial screen by the general dermatologist is T.R.U.E. Test[®] (www.truetest.com; SmartPractice, Phoenix, AZ); recently expanded in 2012, it now comes prepackaged with three adhesive panels containing the 35 most common allergens in the United States plus one negative control. This general screen tests less than 2% of the >3,700 known allergens. T.R.U.E. Test[®] identifies the cause of the allergic contact dermatitis in less than 80% of patients; thus, its limitations should be recognized so that other important allergens, such as newer preservatives, can be appropriately considered when necessary. T.R.U.E. Test[®] now assays for gold sodium thiosulfate as well as group A (tixocortol-21-pivalate), group B (budesonide), and group D2 (hydrocortisone-17-butyrate) corticosteroid-induced allergic contact dermatitis. Additional allergens can be purchased and applied individually enabling patient-tailored patch testing.

A. Application of Screening Agents. Application of T.R.U.E. Test[®] adhesive panels is performed with the three panels side by side. The corners of the panels should be clearly marked with pen/ink in order to facilitate proper alignment of the reading cards days later. The panels are secured into place with tape, and the patient advised to avoid wetting the test area. For patient-tailored/custom screening, apply the test substance(s) to a disk of filter paper bound to plastic-coated aluminum (Al-Test) or in Finn chambers and attach to the skin with occlusive tape. The Al-Test is the standard utilized by the North American and International Contact Dermatitis groups. Alternatively, one can use a 1" square piece of soft cotton (Webril) and cover with occlusive tape (Scanpor) or cellophane and tape. A smaller patch, which may be slightly less effective, may be applied with a 1/4" piece of gauze, linen, cotton, or filter paper and covered with tape (or Dermicel for those who cannot tolerate tape). Liquids and ointments may be applied directly to the cotton or gauze. Volatile liquids should be applied directly to the skin and allowed to dry before being covered. Solids must be powdered before application. Moisten powders and fabrics with water before application. It is critical that the appropriate concentration of the test substance(s) be applied. Too high a concentration may result in a false-positive reaction or may even sensitize the patient.

B. Data Interpretation. Leave the patch test panel(s) or chamber(s) in place for 48 hours (Fig. 49-3). If pain, pruritus, or irritation under a patch is noted, the patient should remove it at once. Readings should not be made until the patches have been off at least 20 to 30 minutes, because positive reactions may not be immediately apparent. Delayed reactions

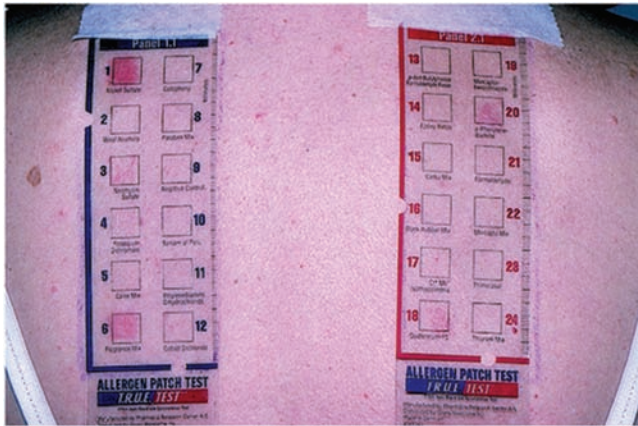


Figure 49-3. A 24-allergen panel T.R.U.E. test, after 48-hour application. Positive reactions are already clearly visible. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

are not uncommon (e.g., gold), and a final reading should be made at 4 to 5 days (96 to 120 hours) and rarely are readings required beyond 7 days (Fig. 49-4). Patch test results are interpreted and denoted using the International Grading System (Table 49-3). Table 49-3 also lists the causes of false-negative and false-positive patch test results. A positive patch test only proves that the patient has a contact sensitivity but not necessarily that the eliciting substance is the cause of the clinical eruption. Relevance of



Figure 49-4. The positive reactions are confirmed at 96 hours. (From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

TABLE 49-3 **International Grading System: Interpreting and Noting Patch Test Results**

?+ or +/-	Doubtful reaction, faint erythema
+	Weak (nonvesicular) reaction—mild erythema and/or papules
++	Strong (edematous or vesicular) reaction—erythema, papules, and/or small vesicles
+++	Extreme reaction—all the foregoing plus large vesicles, bullae, and at times, ulceration
–	Negative reaction
IR	Irritant reaction

Causes of False-Negative Patch Tests

- Low concentration or insufficient amount of antigen
- Improper testing: inadequate occlusion, inappropriate vehicle, wrong site or reading times, deteriorating antigens
- Depressed reactivity from recent use of high doses of systemic steroids or aggressive topical steroid application
- Failure to reproduce true conditions of antigen exposure and lack of heat, friction, or trauma

Causes of False-Positive Patch Tests

- Primary irritant reactions, tape reactions, pressure effects
- Reactions to occlusion: maceration, miliaria, and folliculitis
- Contamination from adjacent site or presence of impurities in the test material
- Multiple concomitant positive patch tests may result in a state of hyperreactivity (excited skin syndrome or angry back syndrome). Subsequent retesting with individual allergens will reveal those that were reactive spuriously⁵

reactions is determined in combination with a patient’s history, cutaneous findings, and contactants.

Once developed, positive reactions may take several weeks to subside. A topical corticosteroid may be used on test sites with active or prolonged inflammation. For positive reactions to T.R.U.E. Test[®] substances, informational handouts on each substance can be accessed (<http://www.true-test.com/panelallergens.aspx>), printed, and provided to the patient to better enable him/her to avoid relevant contact allergen exposures.

ULTRAVIOLET LIGHT THERAPY

I. BACKGROUND Ultraviolet (UV) phototherapy takes advantage of the ability of the energy emitted by ultraviolet light (UVL) to modify cellular metabolism, proliferation, and genetic makeup of epidermal and immune cells leading to profound effects on epidermal turnover and cutaneous immunosuppression. It has become a widely used therapeutic technique with

broad application in many dermatologic disorders with minimal adverse effects. The UV region of the electromagnetic spectrum ranges from the violet end of the visible spectrum (400 nm) to near x-ray region (200 nm). Three ranges comprise the UV spectrum: UVA (1 and 2; 400 to 340 nm and 340 to 320 nm, respectively), UVB (320 to 290 nm), and UVC (290 to 200 nm). Uses, light sources, and adverse effects for each range will be discussed here separately.

UVL is frequently used in numerous dermatologic conditions including but not limited to psoriasis, vitiligo, chronic eczematous dermatoses, generalized pruritus, seborrheic dermatitis, cutaneous T-cell lymphoma, eosinophilic folliculitis, as well as pityriasis rosea and pityriasis lichenoides. The advent of photochemotherapy with the addition of a photosensitizer (psoralen) further broadened UVL utility in refractory or more advanced disease such as in psoriasis, vitiligo, cutaneous T-cell lymphoma, alopecia areata, chronic graft-versus-host disease, and urticaria pigmentosa. UVL phototherapy has also been utilized as a “hardening” tool for prophylaxis of photodermatosis such as polymorphous light eruption and others. UVL phototherapy is preferably administered in hospital- or office-based settings with trained technicians; however, home-based phototherapy can be prescribed in the appropriate setting.

A. Biologic Effects of Ultraviolet Light. Depth of UVL penetration in the skin is dependent on multiple factors including epidermal thickness and melanin content. Relative depth of UVL penetration directly correlates with wavelength: UVA penetrates deeper than UVB, which penetrates deeper than UVC. As such, UVL target effects are different depending on the cell population reached at each level. UV radiation has multiple cellular effects: most notably the formation of photoproducts such as pyrimidine and thymine dimers due to the absorption of the radiation energy by DNA, which is an endogenous chromophore. The formation of these photoproducts alters genetic code and therefore mutates proteins involved in numerous cell functions, including growth, signaling, proliferation, and survival. UV-induced immunosuppression occurs via induction of apoptosis of T cells, stimulation of immunosuppressive cytokine release, and induction of regulatory T cells. The addition of topical or systemic psoralen to UVL potentiates the phototoxicity of UVL leading to a synergistic therapeutic effect. Psoralens are furocoumarins that act by intercalating into DNA. Psoralen-native DNA cross-linking occurs as the UV electromagnetic radiation is absorbed by the psoralen, which leads to inhibition of DNA synthesis, replication, alteration of cytokine production, immune modulation, and cell death. Psoralen has been added to UVA in PUVA (psoralens plus ultraviolet A) and extracorporeal photopheresis (ECP), and more recently nbUVB. For the treatment of psoriasis, PUVA may be combined with other modalities (methotrexate and systemic retinoids), thereby reducing the number of PUVA treatments needed to attain remission, as well as reducing adverse effects from treatment and overall cost.

II. TECHNIQUE

A. Sunlight. Sunlight is often the optimal source of UVL, being the least expensive and most effective under most circumstances. Sun emits radiation with a continuous emission spectrum; however, the ozone layer in the

upper atmosphere absorbs virtually all UVL <290 nm, and clouds contribute to variable sunlight filtering. The erythema dose for a fair-skinned person is 20 minutes at latitude 41° (Boston) at midday in June.

1. Sources. Sunlamp bulbs or units are low-pressure mercury lamps that emit UVL in the sunburn spectrum are used in tanning salons and in patient-care settings for seasonal affective disorder and circadian rhythm dysfunction. Hot quartz lamps (high-pressure, high-temperature mercury arc sources) emit a discontinuous UVL spectrum with bands at 254, 265, 297, 303, 313, and 365 nm but with particular effectiveness in the erythema-producing midrange. The erythema dose is 30 to 60 seconds at 46 cm. Overexposure can lead to severe burns. Hot quartz lamps are generally no longer used in clinical settings.

B. Ultraviolet C. UVC radiation has germicidal and erythemogenic properties and has been used for treatment and prevention of bacterial and fungal infection, antimicrobial treatment of patient-care equipment, and to produce erythema and desquamation in acne patients.

1. Sources. UVC radiation is emitted by low-pressure cold quartz (mercury) lamps. These lamps emit a band of radiation predominantly at 253.7 nm through a quartz envelope filter. The erythema dose is 30 seconds at 25 cm. The advantages are that (i) little or no pigmentation follows the erythema and (ii) severe burns cannot occur, because large increases in exposure time lead to only minimal increases in redness.

C. Ultraviolet B. UVB radiation is responsible for most of the therapeutic effects of sunlight and is the most widely used modality of UVL therapy. Initial UVB dose depends on constitutive melanin content and inducible pigmentation.

1. Sources. Broadband fluorescent sunlamp bulbs (TL-12 bulb; low-pressure, low-temperature mercury arc sources) emit a continuous spectrum (290 to 320 nm) with a peak at 313 nm. The radiation is filtered through calcium, zinc, and thallium phosphate phosphor in the glass envelope. The erythema dose is 90 to 120 seconds at 25 cm.

a. Narrowband UVB (nbUVB; 311 to 312 nm) therapy was developed by Phillips in the 1980s to specifically target the action spectrum of psoriatic skin; however, it has become widely used in other disorders such as vitiligo, cutaneous T-cell lymphoma, and disseminated cutaneous lichen planus. nbUVB is less erythemogenic than broadband UVB and delivers a higher dose of UVB at suberythema levels. It is also reported to be less carcinogenic than broadband UVB. Detailed protocols for UVB treatment of psoriasis have been developed and are standard practices. A minimum erythema dose (MED) must be obtained at baseline for dosimetry; treatments are typically delivered three times a week starting at 50% of the MED and then increasing by 10% to 15% increments. nbUVB bulbs (FL-01) are frequently used as a bank of four 4- or 6-ft-long bulbs for home use or constructed into a light box lined by reflecting metal and many 2-, 4-, and/or 6-ft lamps for office or clinic use. Smaller boxes have been developed for focused treatment of hands and feet, and a hand-held wand has been developed for localized treatment of psoriasis in the home setting. nbUVB phototherapy has also been combined with psoralens. Long-term studies are still required to further

define the efficacy and safety parameters of nbUVB, but it appears to confer less risk than PUVA in terms of carcinogenesis.

b. Excimer Laser. The most novel nbUVB source is the monochromatic excimer laser (308 nm). This is a xenon-chloride gas laser that produces 50 mW/cm² emission at a spot size of <2 cm². The advantages of the excimer laser include higher tolerated doses due to smaller treatment areas, longer duration of remission, fewer total treatments, and less frequent treatments. Excimer is indicated for dermatoses such as stable vitiligo, limited plaque psoriasis, alopecia areata, atopic dermatitis, stage IA cutaneous T-cell lymphoma (CTCL), lichen planus, lichen simplex chronicus, and granuloma annulare.

D. Ultraviolet A. In the presence of a topical or systemic photosensitizer such as psoralen, the long-wave UVA radiation spectrum becomes extremely effective in induction of cutaneous erythema. This combination of light and drug is termed **photochemotherapy** or **PUVA therapy**. In the doses used, neither the drug alone nor the light alone has any biologic activity. PUVA treatment is useful in severe psoriasis and is also effective in some patients with vitiligo, mycosis fungoides, atopic dermatitis, and other inflammatory dermatoses.

- 1. Sources.** Fluorescent black light lamps (FS40BL) (low-pressure, low-temperature mercury arcs) emit a spectrum of 320 to 450 nm filtered through the barium disilicate phosphor in their glass envelopes. The peak emissions vary dramatically, depending on the bulb manufacturer; this variability and their overall low-intensity UVA emission limit their usefulness. High-intensity UVA fluorescent bulbs were developed by GTE Sylvania, and it is these and similar bulbs that are best used in PUVA light boxes.

PUVA treatment boxes are used in hospital clinics and in some dermatologists' offices. One to 2 hours after ingestion of 8-methoxypsoralen (8-MOP), patients are exposed to incremental doses of UVA, starting at 1 to 5 J/cm² (approximately 2 to 10 minutes), depending on the degree of melanization and skin type determination of a minimum phototoxic dose. Dosing of 8-MOP depends on weight (0.4 mg/kg); the pills should be taken 1.5 to 2 hours before light exposure, and dose should be modified for renal or hepatic insufficiency. A fatty meal may enhance absorption. Specific PUVA treatment regimens have been developed to optimize efficacy while minimizing adverse effects. These regimens are divided into an initial clearance phase utilizing more frequent therapy, followed by a maintenance phase. Topical PUVA requires application of 0.1% methoxsalen (Oxsoralen-Ultra) in Cetaphil 20 minutes before UVA. This method minimizes the extent of phototoxicity, and care must be taken to protect the normal surrounding skin. Delivery of psoralens through bath water immersion in a diluted solution of psoralens before the administration of the UVA is also an efficacious method and has been reported to decrease total required radiation. Sunlight-produced UVA can be used with psoralens for the treatment of vitiligo and psoriasis. This technique is potentially dangerous because it is nearly impossible to gauge UVL exposure accurately, and hence, severe burns can result.

a. Extracorporeal Photopheresis is a variation of PUVA in which 8-MOP is administered to leukapheresed blood followed by UVA irradiation and then reinfusion of the blood to the patient. This technique

eliminates the short-term gastrointestinal side effects of oral 8-MOP and decreases long-term complications such as the development of skin cancer and phototoxicity. ECP has been demonstrated to be effective for T-cell-mediated diseases such as CTCL (Sézary syndrome or leukemic forms), systemic sclerosis, graft-versus-host disease, solid organ transplant rejection, nephrogenic systemic fibrosis, and Crohn disease. Standard ECP regimen for CTCL involves treatment on 2 consecutive days every 2 to 4 weeks, for up to 6 months, followed by maintenance therapy tailored to disease severity and course. ECP is thought to work in CTCL by inducing apoptosis in a proportion of tumor lymphocytes, releasing tumor-specific antigens, thereby allowing an antitumor immune response as well as the release of certain cytokines that may mediate antitumor effects.

III. ADVERSE EFFECTS

- A. Ultraviolet A.** The major adverse effect of (P)UVA is erythema, peaking 48 to 72 hours after exposure. PUVA-associated pigmentation appears clinically and histologically similar to normal UVB-induced melanogenesis (tanning). Pigmentation maximizes approximately 5 to 7 days after exposure, is cumulative with repeated PUVA treatments, and is more persistent than a normal suntan. Repeated high-dose PUVA is associated with cataracts and skin cancers (melanoma and non-melanoma). Lentigines and photoaging are also long-term side effects of PUVA. Protection of genital skin during phototherapy sessions and regular skin examinations are recommended. Sunglasses with UVA-blocking properties are recommended on PUVA treatment days. Natural sunlight can exacerbate the phototoxic effect of the psoralen; therefore, extra care should be taken on PUVA treatment days. Short-term side effects of the psoralen include nausea, vomiting, headache, and dizziness. Prophylactic antiemetics may be prescribed on PUVA treatment days. Contraindications to PUVA include lupus erythematosus, xeroderma pigmentosum, pregnancy, and severe kidney or liver disease. Relative contraindications include pemphigus vulgaris, bullous pemphigoid, and history of multiple skin cancers or family history of melanoma. PUVA should also be avoided in children.
- B. Ultraviolet B.** Erythema is the major adverse effect of UVB therapy, peaking 12 to 24 hours after exposure. Other short-term side effects include xerosis, pruritus, and reactivation of recurrent herpes simplex infection. Long-term side effects include photoaging and non-melanoma skin cancer. nbUVB has fewer side effects than broadband UVB because lower total doses of nbUVB are given due to its increased efficacy.
- C. Ultraviolet C.** The major adverse effect of UVC radiation is painful conjunctivitis within seconds of exposure. Protective clothing, glasses, sunscreens are necessary when working around UVC. Minimal erythema and pigmentation are seen with UVC exposure.

PHOTODYNAMIC THERAPY

- I. BACKGROUND** Photodynamic therapy (PDT) is the use of light-activated molecules, called photosensitizers, to selectively destroy a target. The

use of PDT was first reported in the medical literature in the early 1900s and continues today with increasing popularity. The most common dermatologic use for PDT is treatment of actinic keratoses and non-melanoma skin cancers. It is becoming more commonly used for other skin conditions, including inflammatory skin disorders, disorders of the pilosebaceous unit, infections, and cosmesis. PDT is frequently used for the treatment of acne, but has been reported to be successful in a diverse array of conditions from cutaneous sarcoidosis to leishmaniasis.

PDT is a two-step process requiring three key components—a photosensitizer, light, and oxygen. The first step is delivery of the photosensitizer with uptake by target cells. Photosensitizers accumulate at higher concentrations in certain cell types. In the skin, this includes neoplastic cells, epidermal cells, and cells of the pilosebaceous unit. This preferential localization of photosensitizer is the foundation for the relatively selective nature of PDT. The second step is activation of the photosensitizer with a light source. The wavelength of light must fall within the absorption spectrum of the photosensitizer. With absorption of light, the photosensitizer is excited to a higher state, and in turn transfers this energy to oxygen. A low-oxygen environment may dampen the response. Singlet oxygen and other reactive oxygen species are created by this transfer. These highly reactive molecules are responsible for damage within the cell leading to cell death. Aside from cell death, PDT triggers an inflammatory and immune response, which may be responsible for its effects on inflammatory skin diseases and may enhance tumor destruction.

II. TECHNIQUE There is no standardized technique for PDT, and in fact, there are innumerable variations in incubation and light exposure successfully used by current practitioners. Typically, the photosensitizer is placed on the skin and left in place for minutes to hours. After an appropriate incubation time, the patient is exposed to a light source. Appropriate light sources include blue light, red light, intense pulsed light devices, pulsed dye laser, and sunlight.

A. Photosensitizer. Aminolevulinic acid (ALA) is the current photosensitizer of choice for dermatologic indications. Methyl aminolevulinate (MAL) and other photosensitizers are not currently on the market for dermatologic use, but may be options in the future. ALA is not a photosensitizer itself, but is metabolized in the cells through the heme synthesis pathway to form the potent photosensitizer, protoporphyrin IX (PpIX). With the addition of excess ALA, and once cellular iron stores are exhausted, PpIX accumulates. Iron chelators may enhance the response to PDT allowing more buildup of PpIX.

B. Drug Delivery and Incubation. Photosensitizers can be delivered either systemically or topically. For dermatologic indications, ALA is largely delivered topically. Skin preparation techniques can enhance uptake of ALA, including degreasing the skin with acetone scrub, lightly curetting any hyperkeratotic debris, using microchannel devices to create small holes for drug delivery, or occluding the photosensitizer after application. Production of PpIX is temperature dependent. This fact may account for the decreased efficacy of PDT on the extremities, which are usually colder than the core body temperature. Increasing the temperature of the skin during incubation may increase efficacy of PDT on the extremities.

Studied and reported incubation periods for PDT vary from 15 minutes to 18 hours. The current FDA-approved protocol for use of ALA involves a

14- to 18-hour incubation period, but in current practice, 60- to 90-minute incubation times are more common. The incubation time should be increased if the target structure requires deeper penetration of photosensitizer. Three- to 4-hour incubation times are more commonly used for non-melanoma skin cancers like superficial and nodular BCC and for high-dose acne treatments.

C. Light Exposure. The maximum absorption of PpIX is at 410 nm (the Soret band) with smaller peaks between 500 and 635 nm. Longer wavelength light sources, like red light, travel deeper into the skin than shorter wavelength devices, like blue light. Therefore, longer wavelength devices are more appropriate for deeper targets, such as sebaceous glands and non-melanoma skin cancers.

D. Post-procedure Expectations. After treatment with PDT, patients should expect stinging, burning, and sunburn-like erythema followed by crusting, scaling, and peeling lasting about 1 week. Patients treated with longer incubation times and light exposure for the treatment of acne will experience a pustular response a few days after treatment. Patients may also experience prolonged photosensitivity and should be counseled to practice strict sun protection following the procedure. More significant reactions such as blistering and ulceration are possible, but uncommon. Postinflammatory hyperpigmentation may occur, especially after the treatment of acne.

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REFERENCES

1. Head ES, Henry JC, Macdonald EM. The cotton swab technique for the culture of dermatophyte infections—its efficacy and merit. *J Am Acad Dermatol.* 1984;11:797-801.
2. Burke WA, Jones BE. A simple stain for rapid office diagnosis of fungus infections. *Arch Dermatol.* 1984;120:1519-1520.
3. Feuilhade de Chauvin M. New diagnostic techniques. *J Eur Acad Dermatol Venereol.* 2005;19(Suppl 1):20-24.
4. Rietschel RL, Fowler JF, eds. *Fisher's Contact Dermatitis.* 6th ed. Ontario: BC Decker Inc.; 2008.
5. Bruynzeel DP, Maibach HI. Excited skin syndrome (angry back). *Arch Dermatol.* 1986;122:323-328.

Suggested Readings

- Belsito DV. Patch testing with a standard allergen ("screening") tray: rewards and risks. *Dermatol Ther.* 2004;17(3):231-239.
- Caplan RM. Medical uses of the Wood's lamp. *JAMA.* 1967;202(11):1035-1038.
- Cohen DE, Rao S, Brancaccio RR. Use of the North American Contact Dermatitis Group Standard 65-allergen series alone in the evaluation of allergic contact dermatitis: a series of 794 patients. *Dermatitis.* 2008;19(3):137-141.
- Dai T, Vrahas MS, Murray CK, et al. Ultraviolet C irradiation: an alternative antimicrobial approach to localized infections? *Expert Rev Anti Infect Ther.* 2012;10(2):185-195.

- Davis MD, Wang MZ, Yiannias JA, et al. Patch testing with a large series of metal allergens: findings from more than 1,000 patients in one decade at Mayo Clinic. *Dermatitis*. 2011;22(5):256-271.
- Ferguson J. The use of narrowband UV-B (tube lamp) in the management of skin disease. *Arch Dermatol*. 1999;135:589-590.
- Gathers RC, Scherschun L, Malick F, et al. Narrowband UVB phototherapy for early-stage mycosis fungoides. *J Am Acad Dermatol*. 2002;47(2):191-197.
- Gupta LK, Singhi MK. Wood's lamp. *Indian J Dermatol Venereol Leprol*. 2004;70:131-135.
- Habib F, Stoebnier PE, Picot E, et al. Narrowband UVB phototherapy in the treatment of widespread lichen planus. *Ann Dermatol Venereol*. 2005;132(1):17-20.
- Knobler R, Barr ML, Couriel DR, et al. Extracorporeal photopheresis: past, present and future. *J Am Acad Dermatol*. 2009;61:652-665.
- Krob HA, Fleischer AB Jr, D'Agostino R Jr, et al. Prevalence and relevance of contact dermatitis allergens: a meta-analysis of 15 years of published T.R.U.E. test data. *J Am Acad Dermatol*. 2004;51(3):349-353.
- Lapolla W, Yentzer BA, Bagel J, et al. A review of phototherapy protocols for psoriasis treatment. *J Am Acad Dermatol*. 2011;64:936-949.
- MacCormack MA. Photodynamic therapy. *Adv Dermatol*. 2006;22:219-258.
- Man I, Dawe RS, Ferguson J. Artificial hardening for polymorphic light eruption: practical points from ten years' experience. *Photodermatol Photoimmunol Photomed*. 1999;15:96-99.
- Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy. *J Am Acad Dermatol*. 2010;62(1):114-135.
- Morton CE, McKenna KE, Rhodes LE. Guidelines for topical photodynamic therapy: update. *Br J Dermatol*. 2008;159(6):1245-1266.
- Mudigonda T, Dabade TS, Feldman SR. A review of targeted ultraviolet B phototherapy for psoriasis. *J Am Acad Dermatol*. 2012;66(4):664-672.
- Nahass GT, Goldstein BA, Zhu WY, et al. Comparison of Tzanck smear, viral culture, and DNA diagnostic methods in detection of herpes simplex and varicella-zoster infection. *JAMA*. 1992;18:2541-2544.
- Pacifico A, Leone G. Photo(chemo)therapy for vitiligo. *Photodermatol Photoimmunol Photomed*. 2011;27:261-277.
- Rietschel RL. Experience with supplemental allergens in the diagnosis of contact dermatitis. *Cutis*. 2000;65:27-30.
- Ruocco E, Baroni A, Ruocco V. Diagnostic procedures in dermatology. *Clin Dermatol*. 2011;29:548-556.
- Ruocco V, Ruocco E. Tzanck smear, an old test for the new millennium: when and how. *Int J Dermatol*. 1999;38:830-834.
- Sakamoto FH, Lopes JD, Anderson RR. Photodynamic therapy for acne vulgaris: a critical review from basics to clinical practice. *J Am Acad Dermatol*. 2010;62(2):183-193.
- Wetter DA, Yiannias JA, Prakash AV, et al. Results of patch testing to personal care product allergens in a standard series and a supplemental cosmetic series: an analysis of 945 patients from the Mayo Clinic Contact Dermatitis Group, 2000–2007. *J Am Acad Dermatol*. 2010;63(5):789-798.
- Zug KA, Warshaw EM, Fowler JF Jr, et al. Patch-test results of the North American Contact Dermatitis Group 2005–2006. *Dermatitis*. 2009;20(3):149-160.

BOTULINUM TOXIN

I. BACKGROUND Botulinum toxin was first discovered and implicated over 100 years ago as a cause of muscle paralysis. It was not until 1946 however that Dr. Edward Schantz was able to isolate and purify the toxin for therapeutic use. The protein molecule, produced by the anaerobic bacterium *Clostridium botulinum*, is a neurotoxin. The molecule is composed of the neurotoxin itself along with large surrounding protective proteins.

Botulinum toxin blocks the release of acetylcholine at the neuromuscular junction which is critical for neuromuscular transmission. Specifically, botulinum toxin serotype A exerts its effect by cleaving SNAP-25 (synaptosomal-associated protein), a protein required for acetylcholine release. Because of this unique mechanism of action, botulinum toxin was originally used as a treatment for patients with muscular spasm, such as blepharospasm. In 1988, Drs. Jean and Alastair Carruthers made a key observation that periorbital rhytides improved in patients treated for blepharospasm. This observation led to the Carruthers' seminal study in 1992 regarding the cosmetic application of botulinum toxin. Since then, the use of botulinum toxin in noninvasive facial rejuvenation has grown tremendously. Dermatologists now commonly use botulinum in the treatment of hyperhidrosis and dynamic rhytides of the forehead, periorbital area, midface, perioral area, and neck. In fact, botulinum toxin injection is the most common nonsurgical cosmetic procedure performed today. Botulinum toxin has consistently been shown to be a safe and effective treatment when injected by knowledgeable and experienced practitioners.

II. CLINICAL PRESENTATION The typical patient presenting for botulinum toxin injection can range from the young to the elderly. Traditionally in cosmetic use, the patients were often characterized as middle-aged females, but with the significant increase in its popularity, botulinum toxin is now utilized over a much broader demographic. Botulinum toxin injections are used to treat dynamic rhytides or wrinkles formed by muscular contraction. Thus, at rest, wrinkles may not be apparent as it is the contraction of muscles which lead to these lines. The three most commonly treated areas are the glabella, crow's feet, and forehead. There are many other injection points, including the lower face and neck, which can be treated as well.

For patients with hyperhidrosis, obvious sweating may be appreciated at the time of presentation but oftentimes, the patient is only able to give a history of excessive sweating. One survey estimated that up to 2.8% of the US population may be affected. Primary hyperhidrosis is defined as excessive sweating lasting for 6 months or more without an apparent cause and has at least two of the following features: bilateral symmetric sweating, impairment of

daily activities, frequency of greater than one episode a week, positive family history, onset before age 25, and cessation of sweating while asleep.

III. WORKUP Perhaps the most important part of the patient's visit is the preprocedural assessment. It is crucial to assess the patient's expectations and to clearly define the risks and benefits. While the risks of botulinum toxin in cosmetic use are exceedingly rare, when they do occur, the temporary effects can cause significant morbidity in some patients. It is recommended that preprocedural pictures be taken as they can be helpful to show a patient the change that has been made by the procedure.

The clinician should assess the severity of the dynamic rhytides. Some patients have naturally weaker muscles, so the dosing should be adjusted or treatment of that area may be skipped completely. The muscles of the face have a complex interplay with one another so weakening one muscle too much in relation to others can lead to poor cosmetic results if not done correctly. When significant rhytides are noted at rest, a combination treatment with botulinum toxin and soft-tissue augmentation injection or laser resurfacing should be considered. Botulinum toxin injection will help soften wrinkles and prevent the formation of deeper lines formed by dynamic motion, while fillers or lasers can correct static rhytides.

In general, botulinum toxin injection is contraindicated in those with a hypersensitivity to the product or who have an ongoing infection at the injection site. Botulinum toxin injections should also be avoided in women who are pregnant or lactating and those with preexisting neuromuscular conditions.

With hyperhidrosis, the diagnosis relies more commonly on a detailed patient history. To save time, patients can be given a questionnaire to quantify their symptoms on a Hyperhidrosis Disease Severity Scale or a Dermatology Life Quality Index. The minor starch iodine test and gravimetric analysis are more cumbersome tests to perform and used less commonly today. In some cases, insurance companies may subsidize all or part of the treatment if indicated by the hyperhidrosis disease severity scale.

IV. TREATMENT There are seven serologically distinct types of botulinum toxin; however, botulinum toxin A is the only one that is used in cosmetics today. Currently in the United States, there are three commercially available formulations of botulinum toxin A: onabotulinumtoxin A or Botox® (Allergan, Inc., Irvine, CA, USA), abobotulinumtoxin A or Dysport® (Ipsen Biofarm Ltd., Berkshire, UK), and incobotulinumtoxin A or Xeomin® (Merz Pharmaceuticals, Frankfurt am Main, Germany) (Table 50-1). There are even more formulations of botulinum toxin available internationally and more in development, so it is crucial that users are familiar with their properties.

The main difference between the three currently available formulations of botulinum toxin A is the amount of complexing proteins in each product. Botox has the most of all of the products (900 kDa), while Dysport has a more intermediate and variable amount (500 to 900 kDa). Xeomin, the newest addition to the market, is unique in that it is free of any complexing proteins.

The precise role of these complexing proteins remains to be determined but seems to have little effect of the products efficacy. Some have argued that a lower amount of complexing proteins may increase diffusion as one study suggested

TABLE 50-1	Characteristics of Currently Available Botulinum Toxin A Products		
	Onabotulinum-toxin	Abobotulinum-toxin	Incobotulinum-toxin
US trade name	Botox	Dysport	Xeomin
Company	Allergan, Inc.	Ipsen Inc./Medicis	Merz Pharmaceuticals
Molecular weight	900 kDa	500–900 kDa	150 kDa (no complexing proteins)
Units per vial	50 or 100	300 or 500	100
Pharmaceutical form	Powder	Powder	Powder
U.S. FDA-approved indications	Blepharospasm, cervical dystonia, glabellar lines, hyperhidrosis, chronic migraine	Blepharospasm, cervical dystonia, glabellar lines	Blepharospasm, cervical dystonia, glabellar lines
Storage temperature before and after reconstitution	2–8° C/2–8° C	2–8° C/2–8° C	<25° C/2–8° C

an increased diffusion with Dysport. Recent evidence however suggests that the diffusion between botulinum toxin A products is similar. Furthermore, one study showed that after reconstitution, most of the complexing proteins dissociate leaving the native toxin in its free state, and thus these proteins should not have a significant role upon injection. Antibody formation to complexing proteins has been hypothesized as a cause for therapeutic failure after repetitive injections but has not been proven. Therapeutic failure is extremely rare in cosmetic use and has been reported in only a limited number of cases.

The only other significant difference between the products is their dosing. There is still some controversy and debate regarding the exact dosing, but between Botox:Dysport:Xeomin, it appears to be approximately 1:2.5:1. In other words, one unit of Botox would be roughly equal to 2.5 units of Dysport and 1 unit of Xeomin.

Otherwise, the available formulations of botulinum toxin appear to be relatively similar in regard to efficacy, onset of action, duration of action, and safety. The selection of product is largely dependent on patient and physician preference.

The botulinum toxin preparations currently come in powder form (which is almost imperceptible in the vial) and need to be reconstituted prior to use. The package insert for Botox specifically recommends that the product be reconstituted with nonpreserved saline; however, recent studies including a randomized prospective split-face study showed that preserved saline results in significantly less pain on injection and should be considered the reconstituent

of choice. Additionally, the current preparations indicate that after reconstitution, the contents should be discarded if not used within 4 hours. Studies however have shown that the neurotoxin's efficacy remains unchanged after weeks to months and in practice, the majority of physicians store botulinum toxin for over a week.

The three most common areas on injection of botulinum toxin are the glabella, forehead, and crow's feet (Fig. 50-1). These areas can be treated individually or in combination. It is important to understand the anatomy in these

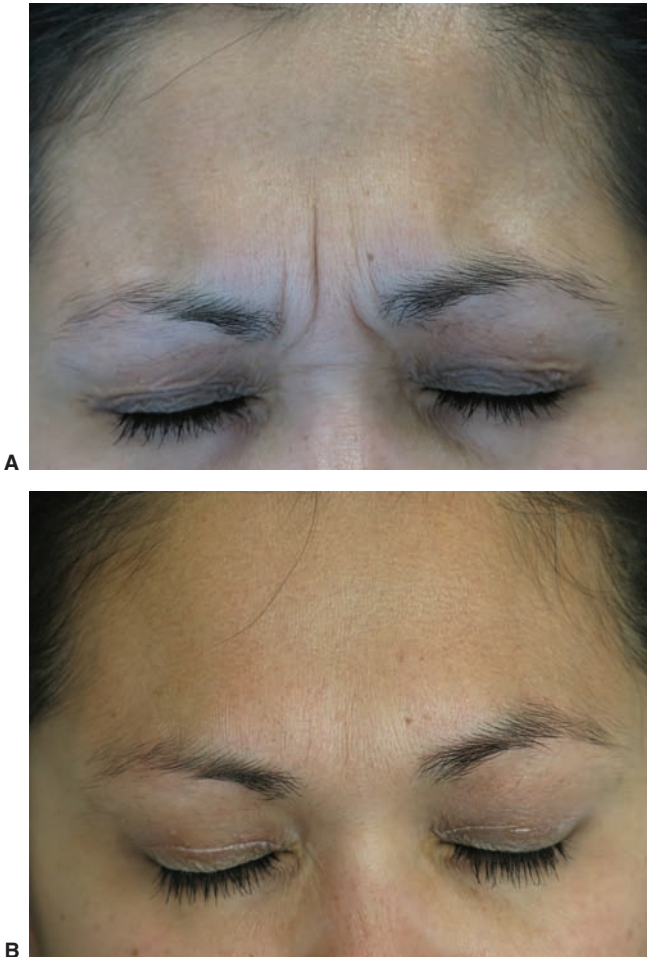


Figure 50-1. Treatment of glabellar lines using onabotulinumtoxin. (A) Before treatment. (B) One week after treatment. (Courtesy of Dr. Jeffrey T.S. Hsu, the Dermatology Institute of DuPage Medical Group in Naperville.)

TABLE 50-2 **Recommendations for Botulinum Toxin Injections in the Three Most Commonly Treated Areas**

Site	Number of Injection Sites	Dosage (number of units based on Onabotulinumtoxin)
Glabella complex	5–7 (men may require more sites)	Women: 10–30 U Men: 20–40 U
Horizontal forehead lines	4–8 (dependent on individual anatomic and aesthetic evaluations)	Women: 6–15 U Men: 6–15 U
Crow's feet	2–5 per side	Women: 10–30 U Men: 20–30 U

(Adapted from Carruthers JD, Glogau RG, Blitzer A. Facial Aesthetics Consensus Group Faculty. Advances in facial rejuvenation: botulinum toxin type a, hyaluronic acid dermal fillers, and combination therapies—consensus recommendations. *Plast Reconstr Surg*. 2008;121(5 Suppl):5S-30S.)

areas to appreciate the interaction of the muscle groups with one another. With proper injections, the eyebrow can be sculpted and elevated, creating an elegant cosmetic result. Recent consensus guidelines in the plastics literature provided recommendations for dosage and injection points in these areas (Table 50-2).

Other areas that can be treated include the nasal dorsum for bunny lines, periorally for vertical rhytides, the chin for dimpling, the neck for platysmal bands, and less commonly the cheek for gummy smiles and masseter hypertrophy. The precise dosages and injection points for treating these areas are beyond the scope of this chapter, especially as these are generally considered more advanced techniques, undertaken after a good degree of experience with injection has been attained.

For axillary hyperhidrosis, 50 units of onabotulinumtoxin (or the equivalent number of units for other botulinum toxin A preparations) are typically injected into each axillae. The needle is injected approximately 2 mm into the dermis to the level of the sweat glands and about 1 to 2 units are deposited in evenly spaced aliquots to cover the affected area. Palms and soles can also be injected for hyperhidrosis although this can be significantly more painful. Ice cubes, air cooling, local anesthesia, and vibratory stimuli can be used to decrease the discomfort. The typical dose for the palms varies but is around 50 to 100 units for each side. Care must be used however not to significantly weaken the intrinsic muscles of the hands. The plantar surfaces typically require slightly higher dosages than the palms.

Following injection of botulinum toxin, muscle paralysis or sweat reduction is not immediate, taking place after about 1 to 7 days. Patients should be warned of this fact as this can be confusing for some. In fact, other than minor swelling from the injection that last about 15 minutes, no other skin changes are generally noted. Patients find this helpful as many can have injections done without disrupting their daily routine. The effect of the toxin peaks at about 2 weeks, and the duration of action appears to be approximately 3 to 4 months.

Higher dosages tend to lead to a longer duration of action up to a certain plateau point. After repeated treatment, there may be a certain degree of muscular atrophy which may lead to a decrease in dosage requirement.

Botulinum toxin has a well-established safety profile when used in cosmetics. After two decades of use, there have been no reported long-term adverse events. When adverse events do occur, they are usually transient and mild in severity. Additionally, while adverse events can occur with any injector and despite all precautionary measures, they are more common in those that are less experienced. The most common adverse events after botulinum toxin injection are injection site reactions and headache. Injection site pain is common and largely unavoidable. Using the smallest gauge needle (30 gauge or smaller) and distracting techniques such as ice application or other physical stimuli can help reduce pain. Some practitioners also use topical lidocaine prior to injection. Bruising at injection sites is more common when treating periorbitally due to the density of vessels in the area. Careful inspection for vessels prior to injection along with pressure after injection can help reduce bruising. Headaches are most common in people who have not received botulinum toxin injections previously. They are generally mild and rarely require analgesics. These headaches invariably resolve within days to weeks. When treating the glabellar complex, eyelid ptosis is another adverse event that may be encountered. Lid ptosis occurs when the neurotoxin unintentionally affects the levator palpebrae superioris, which usually occurs through local diffusion of the toxin. Careful injection placement at least 1 cm above the bony orbit, smaller volumes, smaller dosages, and slower injection speeds can help reduce the incidence of eyelid ptosis. When ptosis does occur, the effect becomes appreciable after 2 to 10 days and lasts for 2 to 4 weeks in general. Apraclonidine 0.5% can be prescribed to stimulate Mueller muscle to lift the eyelid and reduce its severity.

Botulinum toxin injections for cosmetics and in hyperhidrosis are safe and effective in the hands of knowledgeable practitioners. The applications for botulinum toxin injections continue to grow with new formulations becoming available making it crucial to stay up to date in this burgeoning field.

SOFT-TISSUE AUGMENTATION

I. BACKGROUND Dermal fillers provide a safe and effective means for aesthetic soft-tissue augmentation and have experienced a dramatic increase in popularity during the past 10 years. Fillers are used to soften superficial wrinkles, minimize deep folds, and restore volume on the face. The appropriate selection of an agent depends on the size, depth, and location of the volume deficiency (Table 50-3).

In this chapter, soft-tissue fillers are categorized according to their duration of effect as temporary (less than 6 months), long-lasting (6 months to 2 years), semipermanent (2 to 5 years), and permanent (more than 5 years). The degree of overall success is largely proportional to the achievement of realistic and appropriate expectations by both the patient and the physician.

During the initial visit, photographs should be taken to document the patient's appearance prior to the procedure and to facilitate a clear and frank discussion about the patient's areas of concern. To minimize the risk of ecchymosis, patients should abstain from medications that inhibit platelet aggregation for about 10 days prior to injection. Cosmetic makeup and cutaneous

TABLE 50-3 Summarizing Dermal Fillers

Product	Material	Depth of Dermal Implantation	Duration	Relative Advantages	Relative Disadvantages
Juvederm Ultra [®] , Juvederm Ultra Plus [®] , Restylane [®] , Perlane [®] , Belotero [®]	Nonanimal-stabilized hyaluronic acid	Mid	4–6, up to 12 mo	Safe, easy to use, no allergy testing	Pain with injection
Radiesse [®]	Calcium hydroxylapatite	Subdermal	1–2 y	Long-lasting, no allergy testing	Risk of nodule formation, especially lips
Sculptra [®]	Poly-L-lactic acid	Deep or subdermal	Months–years	Long-lasting, no allergy testing	Risk of granuloma formation
ArteFill [®]	Polymethylmethacrylate	Deep to subdermal	“Permanent”	Long-lasting	Requires allergy testing for bovine component
Silikon-1000 [®]	Silicone (polydimethylsiloxane)	Deep to subdermal	“Permanent”	Long-lasting	Some controversy regarding long-term safety and efficacy. Risk of superficial beading, granulomatous reaction, product drift

debris should be removed prior to the procedure. Surface anesthesia with a topical anesthetic or ice for 15 minutes prior to procedure can reduce pain experienced with percutaneous injections, especially in the perioral region. In some cases, nerve blocks and/or regional anesthesia may be required. Proper placement of the filler material is crucial and several injection techniques are used, which include serial puncture, linear threading, fanning, depot injections, and cross-hatching.¹

Temporary Fillers (Hyaluronic Acid Derivatives)

I. BACKGROUND Hyaluronic acid (HA) is an acid mucopolysaccharide that resides in the dermal ground substance and fills the extracellular spaces between collagen fibers. It is a ubiquitous component of the connective tissue matrix in the dermis, and its main biologic function is to create volume and lubricate extracellular structures. During the aging process, the amount of HA in the skin is reduced with resultant loss of tissue hydration and skin turgor, ultimately leading to visible wrinkles.

The hydrophilic nature of HA means that the more concentrated products will tend to imbibe more water, and thus have more tissue swelling following injection. After equilibrium is reached with the surrounding tissue, more concentrated products will maintain more swelling and fullness in the treated area.² Characteristics that make each HA product unique include cross-linking, concentration of the HA, amount of free HA (non-cross-linked), granule size, and G' prime (lift factor).^{3,4}

II. CLINICAL PRESENTATION HAs are approved for correction of moderate-to-severe facial wrinkles and folds but are routinely used for many other indications. They are used off-label for correction of glabellar rhytides, oral commissures, supra-brow area to help elevate the brow, infraocular sulcus for tear trough deformities, and dorsal hands for volume augmentation.

III. WORKUP The products do not require skin testing.

IV. TREATMENT HA derivatives continue to be most widely used soft-tissue fillers. Commonly used Food and Drug Administration (FDA)-approved HA fillers include: Juvederm Ultra® and Ultra Plus®, VOLUMA®, Restylane® and Perlane®, Hylaform® and Hylaform Plus®, Prevelle Silk®, Eleveess®, and Belotero®.

Placement should be in the mid to deep dermis to the point of correction without overcorrecting the defect. They are malleable and contour irregularities are responsive to postinjection manual massage. Duration of augmentation lasts approximately 6 months but may be present for up to 12 months.⁵

Adverse reactions are rare (<2%) and include ecchymoses, acneiform eruptions, injection-site erythema, and reactivation of herpes infection. If filler placement is too superficial, contour irregularity and persistent lumps may occur. There are three possible treatment methods to alleviate these problems: (1) local manual massage; (2) expressing the material by simple incision and drainage; and (3) local injection of small amounts of hyaluronidase to speed resorption by breaking up and dissolving the gel.⁶ When the product is placed too superficially, it may lead to a blue-gray nodule formation or bluish

discoloration in the skin (except for Belotero®). This complication responds to intralesional injection of hyaluronidase or removal of filler after a small incision with an 18-gauge needle or no. 11 blade. Another rare complication is vascular necrosis, especially a risk when injecting the glabellar or alar fold areas.⁷

Long-Lasting Fillers (Calcium Hydroxylapatite)

- I. BACKGROUND** Calcium hydroxylapatite, CaHA (Radiesse®), consists of synthetic microspheres suspended in a carboxymethylcellulose resorbable aqueous gel carrier. Once the carrier dissipates, the matrix composed of 25- to 125- μ m microspheres of calcium hydroxylapatite provides the augmentation effect. This process allows for stimulation of collagen production around the injected microspheres.⁸
- II. CLINICAL PRESENTATION** It has FDA approval for the treatment of deeper facial wrinkles and folds as well as the correction of facial wasting as a result of HIV-associated lipoatrophy. It has also become one of the favorite fillers for hand rejuvenation; however, this indication is not FDA approved.
- III. WORKUP** Skin testing is not required since it is an inert product identical to the primary mineral constituents found in the bone and the teeth.
- IV. TREATMENT** This filler should be deposited deeply at the dermal-subcutaneous junction. It is contraindicated in lip augmentation due to the risk of mucosal granuloma formation and migration of the filler caused by the repetitive contraction of the orbicularis oris. The treatment has proven longevity of up to 1 to 2 years.⁹

Semipermanent Fillers (Poly-L-Lactic Acid)

- I. BACKGROUND** Poly-L-lactic acid (PLA), or Sculptra®, is a synthetic biodegradable polymer that consists of microparticles in a sodium carboxymethylcellulose gel. The material is the same as that used in some suture materials. Occasionally, hypersensitivity granuloma formation may occur.
- II. CLINICAL PRESENTATION** PLA was FDA approved for HIV-associated lipoatrophy. In 2009, it received FDA clearance for the treatment of deep nasolabial folds and facial wrinkles.
- III. WORKUP** The filler must be reconstituted with sterile water as least 2 hours prior to administration with vigorous agitation immediately prior to injection. No skin test is required.
- IV. TREATMENT** PLA is best used for volume enhancement and requires several treatment sessions to achieve the desired effect. Immediate volume expansion is mostly due the fluid of injection, which dissipates over a few days. In the intervening weeks to months, the PLA microparticles are gradually degraded and treated areas undergo expansion of subcutaneous volume via new collagen formation related to the host's immune response to the encapsulated

particles.¹⁰ Clinicians usually space the injections 4 to 6 weeks apart and three injection sessions may be required for the PLA to stimulate new collagen regeneration and reverse the signs of lipoatrophy.

PLA should be injected with a 25-gauge needle into the subcutaneous plane, not into the dermis, to limit the likelihood of developing persistent nodules or papules.¹¹ Smaller bore needles tend to become easily clogged. Patients should be instructed to frequently massage the treated area in the days to weeks following the procedure to prevent the formation of uneven or lumpy fibroplasia. Persistence of augmentation is varied, but some improvement lasts over 2 years.

Permanent Fillers

Polymethylmethacrylate Microspheres

I. BACKGROUND Polymethylmethacrylate (PMMA), Artefill®, is a non-biodegradable, synthetic polymer. The PMMA microspheres are suspended in a rapidly dissolving solution of 3.5% bovine collagen with 0.3% lidocaine added to the syringe. After PMMA is injected, the collagen vehicle is absorbed within 1 to 3 months. New collagen is deposited by the host to encapsulate and engulf the remaining PMMA microspheres. The PMMA microspheres ranging from 30 to 50 μm in size are large enough to avoid phagocytosis but small enough to promote permanent augmentation through fibroplasia.¹²

II. CLINICAL PRESENTATION PMMA is indicated for medium-to-deep wrinkles, folds, and furrows, particularly nasolabial folds. It is also used off-label for glabellar frown lines, radial lip lines, and mouth corners.

III. WORKUP Since the collagen vehicle is obtained from cattle, it is prudent to perform skin testing in order to reduce the risk of an allergic reaction to the bovine collagen.

IV. TREATMENT PMMA, Artefill®, should be placed into the dermal-subcutaneous junction or deeper using the tunneling or linear threading technique. Avoid superficial injections in order to prevent permanent skin surface texture or color change. There is a risk of a hypersensitivity reaction and granuloma formation.

Silicone

I. BACKGROUND Silicone, or polydimethylsiloxane, consists of repeating units of dimethylsiloxane terminated with trimethylsiloxane. Centistoke (cST) refers to the viscosity of silicone oil and is directly related to the chain length of the repeating units. A 1 cST product is equivalent in consistency to water, 350 cST products are oils similar in consistency to mineral oils, and a 1,000 cST product is similar in texture to honey. Pure injectable-grade liquid silicone has never been approved by the FDA and remains prohibited in the United States.

II. CLINICAL PRESENTATION The only FDA-approved form of injectable liquid silicone available for off-label soft-tissue augmentation is Silikon® 1000.

III. WORKUP

The treatments do not require skin testing.

IV. TREATMENT As the placement of the product results in permanent augmentation, there is very little margin for error, and a meticulous technique is essential. Many practitioners prefer to use a glass luer-lock syringe attached to 27- or 30-gauge needle. The silicone is deposited using a microdroplet serial puncture technique, using 0.005 to 0.01 mL aliquots placed at 2- to 5-mm intervals within the dermis without overcorrection. Each treatment should not exceed 0.5 mL of silicone for treating small areas and 2 mL for the treatment of HIV lipoatrophy.¹³ The intervals between sessions are usually monthly until the collagen response and cumulative fibroplasia achieve the desired result.

Common posttreatment events include erythema, edema, and ecchymosis. The incidence of overcorrection with superficial beading, granulomatous reactions, and inflammatory reactions has improved based on the use of only FDA-approved products and adherence to the microdroplet technique.^{14,15}

REFERENCES

1. Rohrich RJ, Nguyen AT, Kenkel JM. Lexicon for soft tissue implants. *Dermatol Surg.* 2009;35(S2):1605-1611.
2. Gilbert E, Hui A, Waldorf HA. The basic science of dermal fillers: past and present. Part I: background and mechanisms of action. *J Drugs Dermatol.* 2012;11(9):1059-1068.
3. Tezel A, Fredrickson GH. The science of hyaluronic acid dermal fillers. *J Cosmet Laser Ther.* 2008;10(1):35-42.
4. Falcone SJ, Berg RA. Crosslinked hyaluronic acid dermal fillers: a comparison of rheological properties. *J Biomed Mater Res A.* 2008;87(1):264-271.
5. Narins RS, Brandt F, Leyden J, et al. A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. *Dermatol Surg.* 2003;29:588-595.
6. Brody HJ. The use of hyaluronidase in the treatment of granulomatous hyaluronic acid reaction or unwanted hyaluronic acid misplacement. *Dermatol Surg.* 2005;31:893-897.
7. Luebberding S, Alexiades-Armenakas M. Safety of dermal fillers. *J Drug Dermatol.* 2012;11(9):1053-1058.
8. Coleman KM, Voights R, DeVore DP, et al. Neocollagenesis after injection of calcium hydroxylapatite composition in a canine model. *Dermatol Surg.* 2008;34:S53-S55.
9. Berlin AL, Hussain M, Goldberg DJ. Calcium hydroxylapatite filler for facial rejuvenation: a histologic and immunohistochemical analysis. *Dermatol Surg.* 2008;34:S64-S67.
10. Jones D, Vleggaar D. Technique for injecting poly-L-lactic acid. *J Drugs Dermatol.* 2007;6:S13-S17.
11. Wildemore JK, Jones DH. Persistent granulomatous inflammatory response induced by injectable poly-L-lactic acid for HIV lipoatrophy. *Dermatol Surg.* 2006;32:1407-1409.
12. De Boulle K. Critical reflections on ArteFill, a permanent injectable product for soft tissue augmentation: mechanism of action and injection techniques, indications, and applications. *Aesthetic Plast Surg.* 2010;34(3):287-289.
13. Prather CL, Jones DH. Liquid injectable silicone for soft tissue augmentation. *Dermatol Ther.* 2006;19(3):159-168.
14. Ellis LZ, Cohen JL, High W. Granulomatous reaction to silicone injection. *J Clin Aesthet Dermatol.* 2012;5(7):44-47.
15. Duffy DM. The silicone conundrum: a battle of anecdotes. *Dermatol Surg.* 2002;28:590-594.

Suggested Readings

- Allen SB, Goldenberg NA. Pain difference associated with injection of abobotulinumtoxin A reconstituted with preserved saline and preservative-free saline: a prospective, randomized, side-by-side, double-blind study. *Dermatol Surg.* 2012;38(6):867-870.
- Carruthers JD, Glogau RG, Blitzer A, Facial Aesthetics Consensus Group Faculty. Advances in facial rejuvenation: botulinum toxin type a, hyaluronic acid dermal fillers, and combination therapies—consensus recommendations. *Plast Reconstr Surg.* 2008;121(5 Suppl):5S-30S.
- Eisele KH, Fink K, Vey M, Taylor HV. Studies on the dissociation of botulinum neurotoxin type A complexes. *Toxicon.* 2011;57(4):555-565.
- Hevia O. Retrospective review of 500 patients treated with abobotulinumtoxin A. *J Drugs Dermatol.* 2010;9:1081-1084.
- Jones D. Volumizing the face with soft tissue fillers. *Clin Plast Surg.* 2011;38(3):379-390.
- Liu A, Carruthers A, Cohen JL, et al. Recommendations and current practices for the reconstitution and storage of botulinum toxin type A. *J Am Acad Dermatol.* 2012;67(3):373-378.
- Pena MA, Alam M, Yoo SS. Complications with the use of botulinum toxin type A for cosmetic applications and hyperhidrosis. *Semin Cutan Med Surg.* 2007;26(1):29-33.
- Saedi N, Rotunda A, Jones DH, et al. Soft tissue augmentation. In: Bologna JL, Jorizzo JL, Schaffer JV, eds. *Dermatology*. 3rd ed. Philadelphia, PA: Elsevier; 2012.

I. GENERAL PRINCIPLES OF TOPICAL ABSORPTION Topical formulations are a mainstay treatment for skin disorders, as they offer targeted dose of medication where needed and thereby reduce side effects and toxicity to other organs. Absorption through the skin depends on properties of the skin and the medication. Skin thickness and hydration can vary considerably depending on individual age and skin disorder as well as the particular body site of interest. Generally, absorption occurs more readily in thin and well-hydrated skin.

Chemical properties of the drug, including **molecular size**, **lipophilicity**, and **concentration** of active ingredients, also influence medication absorption. Smaller sized particles, greater lipophilicity, and higher concentrations are associated with better penetration and absorption.

Consequently, the practitioner must choose the topical formulation of choice optimized for a particular site of the body or type of skin condition. For example, a medication for chronic scaly skin lesions should have high lipophilicity and moisturizing properties to maximize penetration of active ingredients into the skin. In general, conditions with acute inflammation are treated with aqueous drying preparations, whereas chronic inflammation is treated with greasier, more lubricating compounds.

II. TYPES OF TOPICAL MEDICATIONS (Table 51-1) Topical drugs are chosen based on their active ingredients and vehicle (base which includes inactive ingredients), as either variables can be manipulated to optimize potency of treatment. While the medication itself will directly target the condition, the vehicle has an equally important (though often overlooked) role in altering the composition and overall delivery of the active ingredients. In fact, differing vehicles between generics and their corresponding brand name drug cause decreased potency despite having equivalent active ingredients. This section will provide an overview of the different types of dermatologic topical preparations, including the following formulations (in order of most drying to hydrating): powders, liquids, gels, creams, and ointments. Though most topical medications fall into one of the aforementioned categories, a select number do not; this section will also touch upon these few.

A. Powders are dried forms of substances, with either inert or active ingredients, used primarily in intertriginous areas to reduce moisture, maceration, and friction. They may be nonabsorptive, making the skin slippery (talc), or absorptive (starch). Talc can cause a granulomatous reaction in wounds, and starch may be metabolized by organisms to cause an increase in *Candida* overgrowth. Powders should be used only in intact skin and avoided at any site with maceration, ulceration, or erosion.

B. Gels are drying agents best used in hairy or oily areas. These thickened semisolid emulsions liquefy upon contact with the skin, usually drying to

TABLE 51-1 Common Topicals

	OTC	Prescription
Powders	Talc, Baby powder	Nystop
Liquids	Calamine lotion, Burow solution, Domeboro solution	Diclofenac 1%, Nex crème rinse 1%
Gels	PrameGel, aloe vera gel	Isotrex 0.05%, Differin 0.3%, Epiduo 0.1%/2.5%, Duac 1.2%/5% gel
Creams	Cold cream, hydrocortisone 1%	ReTrieve 0.05%, Retin-A, Doxepin 5% cream
Ointments	Petroleum jelly, neosporin, resinol medicated ointment	Dermol 0.05%, Diprosone 0.05%, Bactroban 2% ointment
Pastes	Zinc oxide paste	Triamcinolone paste
Soaks	Oilated Aveeno, Alpha keri oil bath	
Med soaps	Dial (1.5% triclosan), Safeguard (1.5% tricloban)	Benzac wash (5% benzoyl peroxide)
Med shampoos	T-Sal (3% Salacid), Selsun Blue (1% selenium sulfide), Head and Shoulders (1% zinc pyrithione)	Selseb (2.25% selenium sulfide), Nizoral (2% ketoconazole)

a thin and greaseless film. Since gels often contain alcohol and/or acetone, they often cause relatively high rates of irritation. Therefore, they should be avoided in sites with fissures, erosions, or macerations. The skin does not absorb gel as well as other preparations. Gels are often prescribed for conditions involving hands, feet, and the trunk.

- C. Liquids** are the least potent and moisturizing of all wet vehicles (which include ointments, creams, and gels). This category includes lotions, solutions, sprays, foams, and aerosols. Liquids dry and evaporate quickly, making them useful in oily and hairy areas of skin. They are also effective for cooling inflamed or oozing lesions, such as those caused by contact dermatitis, athlete's foot (tinea pedis), and jock itch (tinea cruris). Liquids should be avoided at sites of fissures and erosions, as they can cause moderate irritation.
- D. Creams** can be used anywhere on the body, making them the most versatile and cosmetically appealing of the vehicles. These commonly used preparations are semisolid emulsions of oil in water (O/W). Because of their oil content, they have greater viscosity and hydrating properties than gels and liquids. Similar to powders and gels, it is generally recommended to avoid application at macerated sites.
- E. Ointments** are the best vehicles to deliver active ingredients into the skin. They are most effective for dry and thick skin such as that of hyperkeratotic and lichenified lesions (e.g., psoriasis, lichen simplex chronicus, and

chronic eczema). Though they are the least irritating of the bases listed thus far, they should still be avoided in oily, infected, oozing, and intertriginous areas. Ointments are also the most occlusive, messy, and difficult to wash off. Some commercially available ointments include Aquaphor, Polysporin, and Vaseline.

F. Pastes are useful for conditions needing increased breathability of the skin and consist of mixtures of a fine powder into an ointment, usually petrolatum. Typically an ointment is mixed with a fine powder, which constitutes 20% to 50% of the paste. Commonly utilized powders include zinc oxide, talc, starch, bentonite, aluminum oxide, or titanium dioxide. Since the addition of powder improves the porosity of the vehicle, pastes are useful for diaper and intertriginous dermatitis. Pastes should be applied evenly with a tongue blade or finger and may be removed most easily with a cloth soaked in mineral or vegetable oil.

G. Wet Preparations. Ranging from baths to wet dressings, wet preparations are water-based vehicles that function to cleanse and cool the targeted areas of skin.

1. Wet Dressings are wet compresses indicated for acute inflammatory conditions, erosions, and ulcers. They provide relief by cooling the area through evaporation, decreasing local blood flow to reduce inflammation, and cleansing the skin of exudates, crusts, and debris to help maintain the drainage of infection. Although various medicaments and antibacterial substances may be added for specific causes, water is by far the most important ingredient of wet dressings. Wet dressings covered by an impermeable cover (closed wet dressings) retain heat and prevent evaporation. Long-term use may cause maceration.

2. Baths and Soaks utilize substances such as oatmeal and cornstarch to relieve widespread eruptions, most commonly conditions such as chicken pox lesions. They have a cooling and drying effect on the skin to reduce itching and relieve oozing erythematous eruptions. Aveeno Colloidal Oatmeal is a commercially available product often used to soothe eczematous conditions.

Bath oils, usually containing a mineral or vegetable oil as well as surfactant, added to tub water can help prevent drying of the skin. They either disperse throughout the bath or remain on the surface of the water to later coat the body surface upon leaving the tub. Bath oils can produce a mild pruritus immediately after their use. The following are some common preparations: Alpha Keri, Aveeno, Lubriderm, Nutraderm, and RoBathol.

H. Other Types of Topical Medications come in the form of soaps, shampoos, and protective coverings for the skin.

1. Medicated Soaps are often antimicrobial, containing topical antiseptics such as carbanilide, triclocarban, and the substituted phenol triclosan. They have some deodorant action by inhibiting bacterial growth. Representative soaps include Clearasil Antibacterial (triclosan), Coast (tricloban), Dial (1.5% triclosan), Irish Spring (0.75% tricloban, 0.25% triclosan), Safeguard (1.5% tricloban), Zest (tricloban), Jergens clear complexion (triclocarban), Lever 2000 (triclosan), and Lifebuoy III (triclosan).

2. Medicated Shampoos contain ingredients such as coal tar, selenium sulfide, and zinc pyrithione for simultaneous cleansing and treatment of seborrheic dermatitis, dandruff, psoriasis, and/or tinea versicolor.

3. **Adherent Dressings** are coated with a substance in tincture of benzoin and flexible collodion that helps keep the affected skin area dry. They function to further prevent irritation of the adjoining skin tissues.

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Suggested Readings

- Begoun P. *Don't Go to the Cosmetics Counter Without Me*. 4th ed. Tukwila, WA: Beginning Press; 1999.
- Macneal R. *The Merck Manual Home Health Handbook*. Whitehouse Station, NJ: Merck & Co Inc.; 2006.
- Schoen LA, Lazar P. *The Look You Like: Medical Answers to 400 Questions on Skin and Hair Care*. New York: Marcel Dekker Inc.; 1990.

52

Amount to Dispense

Quynh-Giao Ly Nguyen

A. QUANTITY

In order to maximize their use and efficacy, topical drugs should be applied in a way that is precise and consistent. It is important that this process is standardized, since under- or overapplication can lead to inadequate amounts of medication dispensed or unnecessary risk of medication side effects, respectively. Normally, topical medications should be applied to the skin in a thin layer. One gram of cream will cover an area of skin approximately $10\text{ cm} \times 10\text{ cm}$, approximately 100 cm^2 , assuming a layer $100\text{ }\mu\text{m}$ in thickness. That same amount in an ointment vehicle will cover an area 5% to 10% larger. For all types of semisolid topicals, the fingertip unit (FTU) is a practical guide for the amount of drug to cover a specific region. One FTU represents the amount of topical drug expressed from a tube with a 5-mm-diameter nozzle that is applied from the distal skin crease to the tip of the index finger. This amount, roughly 0.5 g, is enough to treat twice the area of skin covered by the palmar surface of a hand. In other words, $1\text{ FTU} = 0.5\text{ g} = 2\text{ hand areas}$, $2\text{ FTUs} = 1\text{ g} = 4\text{ hand areas}$, and so forth. With this estimate, approximately 20 to 30 g of cream or ointment will cover an adult once. It is important to correctly prescribe the amount of medication needed for a full treatment course.

Table 52-1 provides conservative estimates for dispensing appropriate quantities of medication.

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Suggested Readings

Begoun P. *Don't Go to the Cosmetics Counter Without Me*. 4th ed. Tukwila, WA: Beginning Press; 1999.

Schoen LA, Lazar P. *The Look You Like: Medical Answers to 400 Questions on Skin and Hair Care*. New York: Marcel Dekker Inc.; 1990.

TABLE 52-1		Amount of Topical Medication Needed for Single or Multiple Application(s)			
Area Treated	One Application (g)	b.i.d. for 1 wk (g)	t.i.d. for 2 wk (g)	b.i.d. for 1 mo (g)	t.i.d. for 6 wk (g)
Hands, head, face, and anogenital area	2	28	90 (3 oz)	120 (4 oz)	270 (9 oz)
One arm, anterior or posterior trunk	3	42	120 (4 oz)	180 (6 oz)	360 (12 oz)
One leg	4	56	180 (6 oz)	240 (8 oz)	540 (18 oz)
Entire body	30-60	420-840 (14-28 oz)	1.26-2.52 kg (42-84 oz; 2.5-5 lb)	1.8-3.6 kg (60-120 oz; 3.75-7.5 lb)	3.8-7.5 kg (126-252 oz; 7.5-15 lb)

GENERAL PRINCIPLES OF NORMAL SKIN CARE

A variety of skin care products are available on the market, often touting skin-revolutionizing claims, to the point where a product exists for almost any kind of skin care concern. Despite the overwhelming number of products and advertising claims, the recommended skin care regimen is much less complex. Routine care of normal skin focuses on keeping it clean, balanced, protected, and free of irritation. These goals can be achieved with a simple regimen, often of three or fewer steps, performed once or twice daily, and adjusted accordingly to seasonal weather changes. The steps in this regimen include gentle cleansing, moisturizing, and protecting the skin from ultraviolet (UV) rays—the last of which can be skipped at night. In addition to discussing the principles underlying the recommended regimen, this section will analyze various popular skin care treatments available. A brief subsection on hair and scalp care is also included.

An important caveat to this section is that while “normal” skin refers to skin not affected by any disease process, it still encompasses a diversity of skin textures, colors, and complexions. The principles in this section are applicable to almost every “normal” skin type.

I. SKIN NUTRITION

- A. Supplements.** Dietary supplements may be beneficial in cases of difficulty obtaining nutrient(s) through normal dietary means. The risk of toxicity may outweigh the potential benefits to normal skin. Except in nutritional disorders such as avitaminoses (e.g., pellagra), there is no convincing proof that any dietary supplement can enhance skin, hair, or nail growth.
- B. Topicals.** Topical application delivers nutrients more quickly and effectively than dietary supplementation. However, since replicating cells in the skin, hair, and nails receive their nutrition from deep dermal vasculature, external application of nutrients—including antioxidants, amino acids, collagen, ribonucleic acid, and elastin—may not penetrate or stay long enough to have more than a transient effect. Even the best topicals only affect the cells near the surface, thus eventually losing the topicals’ imparted benefits once shed. Despite their limitations, the benefits of topicals loaded with antioxidants still make them worthwhile. For instance, vitamin E, which is stored in the stratum corneum, forms the first line of antioxidant defense and further has a protective effect on cellular membranes. In addition to vitamin C, vitamin E has been shown to improve the skin’s moisture retention and decrease free-radical damage.
- C. Lifestyle.** The majority of the skin’s nutrition is internally derived, and driven primarily by genetically determined physiologic factors and secondarily by

dietary intake. Though one cannot change their genetic makeup, they can optimize the health of their skin through prudent lifestyle choices such as getting enough rest and relief from stress.

- D. Diet.** A positive change in diet can manifest as skin changes within a few weeks. Antioxidants such as vitamin A are present in fish as well as yellow and green vegetables and have been shown to affect growth and differentiation of human keratinocytes *in vivo*, promoting cell turnover. Citrus fruits and sweet potatoes are foods rich in vitamins C and E, respectively, and are known to have a calming effect on skin. Melons are lauded for their high water content. In general, a diet high in vegetables, fruits, nuts, fish, and water can promote healthy skin.

II. CLEANSING THE SKIN

- A. Formulation.** As the first step in normal skin care, cleansing lifts away pore-clogging buildup and stimulates circulation to the skin. The market offers a variety of cleansers for the face, from soaps to creams and lotions. Generally, one should consider skin type, environment, and makeup when choosing a cleanser, as no one formula will work best on everyone. Soap-and-water cleansing will remove most substances from the skin, including dirt, sweat, bacteria, and oils. Dry skin benefits more from superfatted soaps, which contain more fatty materials such as cold cream, cocoa butter, and lanolin. Transparent soaps, containing glycerin, are another option for those with dry and/or sensitive skin. Meanwhile, oily skin cleanses better with soaps high in surfactant. Those living in harsh environmental conditions, such as windy and/or low humidity cities, may wish to consider formulations for dry/sensitive skin. Those who use waterproof makeup may look to creamy formulations, which more easily remove oil-soluble ingredients. In many instances, an effective regimen consists of removing makeup with a cleansing cream followed by soap-and-water to clean the skin. “Synthetic soaps” are a more recent option. They are formulated with synthetic detergents that claim to be gentler and less drying on the skin.
- B. pH.** The pH of normal skin at its surface is approximately 5.5 (though some studies have reported a value below 5 for natural skin without any contact with product or water). Most natural soaps, which contain surfactants, are much more alkaline at pH 9 to 10 and transiently increase skin pH. This finding has been used in marketing for many synthetic soaps to promote their more neutral pH (usually below 7) and therefore superior efficacy. In general, maintaining skin at a lower pH has been linked to better skin health, preserving resident skin flora and reducing the risk of irritation. Recent studies have shown that Dove, a primarily synthetic soap of neutral pH, was the least irritating among 18 cleansers tested. At the same time, not enough evidence supports that other soaps, aside from potential side effects of irritation, are harmful to normal skin. It should be noted that even water will increase skin pH transiently. Nevertheless, a pH neutral cleanser may be a reasonable starting point when choosing a formulation.
- C. Frequency.** Excessive washing with soap or detergents can lead to dryness of the skin, an effect compounded in areas of high wind and low relative humidity. The use of a “mild” soap and a reduction in the number of washings to once or twice daily will minimize the drying effects. Those who must

wash their hands frequently are advised to use as little soap as possible and to apply an emollient such as petrolatum after washing.

- D. Deep Cleansing.** Methods of deep pore cleansing (e.g., “facials”) may decongest skin, temporarily improving appearance. No long-term benefits of this have been demonstrated.

III. MOISTURIZING THE SKIN

A. Formulation. Moisturizers or emollients function to increase the stratum corneum's moisture level by (1) attracting water to the skin, (2) decreasing friction between the lamellae of the stratum corneum (lubrication), and/or (3) forming a seal to lock in moisture. Though used synonymously with “moisturizers,” *emollients* are the actual lubricating agents in moisturizers that can be used alone on the skin. Petrolatum, for example, is a very effective and inexpensive emollient. Effective moisturizers usually contain a substantial amount of emollients as well as water-binding agents (humectants), anti-irritant substances, and antioxidants. It is best to apply a moisturizing agent after each cleansing, when skin is still damp. Selecting which moisturizing agent to use will largely depend on personal preference.

- 1. Emollients** are usually the most inexpensive and effective way to lubricate the skin, but may not be the most cosmetically acceptable. Ingredients such as plant oils, mineral oil, shea butter, cocoa butter, petrolatum, and lanolin fall into this category. Emollients mainly serve to transiently make skin more pliable and supple. Since they contain little to no synthetic ingredients, including potentially irritating fragrances, emollients are the simplest option for moisturizing the skin. The greasy nature of some emollients may clog pores and cause acne.
- 2. Moisturizers** contain mixtures of ingredients, including—but not always limited to—emollients, humectants, anti-irritants, topical exfoliants, smoothing agents, and antioxidants. They are formulated as either oil-in-water (O/W) or water-in-oil (W/O) emulsions, the latter of which is heavier but longer-lasting. W/O emulsions are generally nighttime creams, indicated for drier skin types, whereas O/W emulsions make up lighter, daytime lotions. Another subset of moisturizers includes the “oil-free,” which in place of emollients contain synthetic ingredients such as silicones, for oilier skin types. Generally, a good moisturizer will contain a high amount of emollients, humectants, anti-irritants, and antioxidants, while minimizing the amount of other unnecessary ingredients. Of these moisturizers, the efficacy of one over another depends on individual skin type and may further vary as skin changes from season to season.

B. Specific Benefits. Though not necessarily skin revolutionizing in aging or wrinkles, various ingredients in moisturizers are implicated to improve the appearance and prevent future damage of skin. A few notable ones are listed: Exotic oils such as jojoba and mink oil are effective emollients that have proven to be relatively stable to oxidation; it is not clear that their topical application have special benefits beyond this. Humectants such as lactic acid, glycerin, and urea enhance the water-bearing capacity of the stratum corneum. Vitamins C and E synergistically help prevent free-radical damage. Vitamin A derivatives (e.g., retinol) can stimulate cell turnover. Green tea and aloe have soothing, anti-inflammatory effects on the skin.

Argan oil is a noteworthy emollient and has protective properties for skin and hair. Moisturizers rich in these ingredients are particularly beneficial at night when the skin is repairing itself. Daytime moisturizers should contain adequate UVA and UVB protection or be paired with an effective sunscreen.

- C. Packaging.** Many ingredients are exceptionally unstable and break down with sunlight and air exposure. This principle puts in favor squeeze-tube and dispenser-pump packaging over jar-packaging.

IV. PROTECTING THE SKIN

- A. UV Protection.** Widely known to help prevent UV-associated photoaging, photosensitivity, and skin malignancies, the application of UV protection (e.g., sunscreen) is indispensable in daily skin care. The use of tanning beds, which concentrate UV rays thereby compound their damaging effects, should be absolutely avoided.

- 1. Active Ingredient.** The ingredients avobenzone and zinc oxide represent the best sunscreens on the market in broad-spectrum protection against UVA (290 to 320 nm) as well as UVB (320 to 400 nm) wavelengths. Another ingredient, titanium oxide, is lauded for its protection of shorter wavelengths but pales in comparison to the previous two at wavelengths >360 nm. Zinc oxide and titanium oxide are common “physical blockers” that reflect UV rays.
- 2. SPF.** The first sign of “damage” from UV rays is erythema (reddening) of the skin. The SPF number correlates with the time frame it takes for a person to produce erythema when a particular sunscreen has been applied. A higher SPF represents stronger and longer sun protection. In general, fairer-skinned individuals require SPF 30 or greater, whereas more pigmented skin may achieve adequate protection at SPF 15. The trade-off with higher SPF includes increased risk for potential irritation (due to higher concentrations of active ingredients) and decreased natural production of vitamin D₃. Also, products with higher SPF may be less desirable because of their steeper cost and thicker formulation. However, the greater protection conferred by higher SPF is not only worth the trade-off but can also compensate somewhat for sunscreen underapplication, which frequently occurs.
- 3. Usage.** It should be noted that a sun protectant only achieves its SPF rating when applied properly. One ounce (approximately a shot glass worth or 2 mg/cm²) of sunscreen is recommended for adequate head-to-toe protection, though most people apply less than half this amount. The sunscreen should be applied 30 minutes before engaging in outdoor activity in order to allow enough time for penetration into the deeper layers of skin. The ears, back of the neck, backs of hands and arms, tops of feet, and bald areas of scalp should not be overlooked.

V. ADDITIONAL SKIN CARE STEPS

- A. Toners** are lotions or washes designed to shrink pores (“refine skin”) and balance skin pH after cleansing. They are composed primarily of water, alcohol, or witch hazel. The mildest form, called skin bracers or fresheners, contain

a humectant and little to no alcohol, thus can be used by most skin types. Skin tonics are slightly stronger with more alcohol and target oilier skin types. Lastly, astringents, indicated exclusively for oilier skin, contain a high proportion of alcohol or witch hazel in addition to antiseptic ingredients. All toners work by irritating skin around pores to make large pores appear less obvious. They also remove residue from cleansing and, due to their acidic nature, help restore skin back to its natural pH. However, their effects can backfire, triggering more oil production as skin attempts to compensate for the moisture-stripping effects of alcohol. Overall, the skin benefits of toners are minimal and generally outweighed by the potential irritation and side effects.

- B. Exfoliants** function to remove dead cells from the skin's outermost layer (stratum corneum) so as to smooth and soften the skin. This process can be achieved through mechanical exfoliants, which physically scrub away dead skin, or mild chemical exfoliants that cause the skin to flake or peel. Stronger chemical exfoliants penetrate deeper layers, though still work by the same process. Both physical and chemical methods essentially injure the skin to indirectly stimulate skin healing and regeneration—achieving significant results when done correctly. However, these processes are difficult to precisely control and have potential for causing serious harm, e.g., severe scarring, to the skin.
- C. Masks**, which may contain an absorbent clay or synthetic resin, form a film that tightens on the skin as it dries. This can produce mild irritation, which makes the face rosy and the pores transiently smaller. The added benefits of facial masks are few since they do not penetrate the skin any deeper than regular cleansers. Most of the benefits are psychological, evoked with the tightening and tingling sensation produced as the mask dries.
- D. Serums** are liquids with concentrated active ingredients that are applied after cleansing and before moisturizing. Because they contain a more finely milled formula with fewer filler ingredients than most moisturizers, serums claim to better penetrate and deliver nutrients to the deeper layers of the skin. Serums alone appear to effectively address specific needs of the skin, such as managing erythema in aging skin. Whether a serum is necessary in addition to a nutrient-rich moisturizer has yet to be substantiated.
- E. Drying Agents** such as talcum powder, cornstarch, and aluminum salts (found in antiperspirants) function to remove excessive moisture from the skin surface. They are most useful for intertriginous areas. When used in moderation, they can help prevent irritation and maceration of the skin.

VI. HAIR AND SCALP CARE

- A. Shampooing.** This removes exfoliated skin and debris from the scalp.

- 1. Formula.** Shampoos employ detergents such as sulfates in order to form a thick, viscous liquid that lathers and cleans. Since sulfates are often more alkaline than soaps (the strongest being sodium lauryl sulfate and ammonium lauryl sulfate), overuse of these shampoos can cause hair cuticles to become rough and dull. This can be reversed by acid hair rinses, which remove mineral deposits and smooth hair cuticles, and further reduce swelling of the hair shaft to make the hair appear sleek and shiny. Sulfate-free shampoos or baby shampoos are the mildest of the shampoos.

2. **Frequency.** Maintaining good hair hygiene can be sufficiently achieved by shampooing once or twice a week. Though daily shampooing of normal scalp and hair will not ordinarily cause hair loss, it can lead to hair dryness and breakage that can mistaken for hair loss. Dry shampoos, composed of an absorbent powder and mild alkali, may help remove oils, dirt, and odors on days when normal shampooing is skipped.
- B. **Conditioning** rinses put an oily coating back on the hair to replace that removed by the shampoo, thus adding luster, softness, and manageability. They can vary in consistency, ranging from light leave-in conditioners to thick pack conditioners. In addition to ingredients that change the electrical charge, they can also contain emollients, humectants, detanglers, surfactants, antistatic agents, and reconstructors. These rinses are useful for hair damaged by heat/chemicals, physical abuse, or excessive exposure to UV light or harsh weather.
- C. **Combing and Brushing** stimulate scalp circulation and distribute hair oils to help confer a healthy sheen. Detangling with a wide-toothed comb is preferred for thicker, curly hair, whereas straight hair may benefit more with a paddle brush. Wet hair of any type should be treated with care, as it is very elastic and may more easily break when stretched.
- D. **Styling.** Prolonged use of heat and chemicals, particularly permanent waving solutions, can cause hair to become dry and brittle. This damage, however, only alters hair already grown out of the follicle and does not affect hair growth. However, physical abuses to hair, such as hairstyles that promote prolonged traction near hair roots, can cause follicular scarring and permanent alopecia.

VII. ADVERSE REACTIONS

- A. **Cosmetic Allergies.** All products hold a potential for causing an allergic reaction, either immediately or delayed. The former is more commonly reported, likely because the offending culprit is harder to pinpoint with a delayed reaction. Since skin changes with seasonal and hormonal fluctuations, a long history of problem-free use does not guarantee that a particular product will not cause an allergic reaction. The skin may suddenly become intolerant to a long used product. This may be due in part to the changes in the product itself, as manufacturers can make minor alterations to formulations without concomitant labeling changes. For example, manufacturers are not required to disclose addition of a single new fragrance, which may contain >200 chemicals. In fact, fragrance is the number one cause of allergic reactions in cosmetics. Even products labeled “fragrance-free” may contain fragrances to cover the chemical smell of other ingredients. Thus, the investigation of cosmetic allergies is complex and may require discontinuation of all current cosmetics if a culprit cannot be easily detected.
- B. **Hypoallergenic Cosmetics** are theoretically made of highly purified ingredients, designed to eliminate the most notorious allergy-producing compounds. However, any product may legally be labeled “hypoallergenic” and still contain components allergenic to some individuals. Usually, though, cosmetic companies screen and test their products quite thoroughly to eliminate potential allergens. The rate of adverse reactions to hypoallergenic

cosmetics of all types, even the inexpensive ones, is quite low compared with nonhypoallergenic products.

C. Patch Testing. Persons with suspected allergies to cosmetic ingredients will often benefit from patch testing. Patch testing is particularly beneficial for individuals with multiple sensitivities or with sensitivity to an undetermined compound.

D. Acne Cosmetics describes comedones caused by comedogenic substances found in a cosmetic product, especially emollients and oil-based makeups. Notoriously comedogenic compounds include sodium lauryl sulfate, isopropyl isostearate, isopropyl myristate, butyl stearate, hexadecyl alcohol, lauryl alcohol, oleic acid, lanolin, and cocoa butter. As an extra precaution to prevent acne cosmetics, one may choose to use water-based cosmetics, usually labeled as “oil-free.” Those looking to take further precaution may look for cosmetics with both “oil-free” and “noncomedogenic” on their labels.

VIII. CONCLUSION The recommended regimen consists of two to three basic steps: cleansing, moisturizing, and protecting the skin from harmful UV rays in the daytime. However, choosing products in each category can still be overwhelming. It is difficult to recommend a specific product, as no product will universally work best on every person. Ultimately, the choice of one formulation over another depends on personal preference.

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Suggested Readings

- Burns DA, Breathnach SM, Cox N, Griffiths CE. *Rook's Textbook of Dermatology*. Oxford, UK: Blackwell Publishing Ltd.; 2010.
- Cole C, Ouyang H, Stanfield J, Appa Y. The relevance of high SPF products: high SPF sunscreens help compensate underapplication. *J Am Acad Dermatol*. 2011;64(2):1, P3104.
- Draelos ZD. Essentials of hair care often neglected: hair cleansing. *Int J Trichol*. 2010;2(1): 24-29.
- Guillaume D, Charrouf Z. Argan oil and other argan products: use in dermocosmetology. *Eur J Lipid Sci Technol*. 2011;113:403-408.
- Lambers H, Piessens S, Bloem A, Pronk H, Finkel P. Natural skin surface pH is on average below 5, which is beneficial for its resident flora. *Int J Cosmetic Sci*. 2006;28: 359-370.
- Noreen HN, Schlepp, SL. Sunscreen use: an overview. *Plast Surg Nursing*. 1999;19(3): 148-151.
- Schoen LA, Lazar P. *The Look You Like: Medical Answers to 400 Questions on Skin and Hair Care*. New York: Marcel Dekker Inc.; 1990.

I. BACKGROUND The sun radiates a broad system of energy that may be categorized in terms of the wavelength of its electromagnetic waves. The radiation reaching the earth's surface may be subdivided into infrared (800 to 1,700 nm), visible (400 to 800 nm), and ultraviolet (290 to 400 nm). Ultraviolet radiation (UVR) can be further divided into three bands (Table 54-1).

Ultraviolet A (UVA) radiation (320 to 400 nm) causes immediate pigment darkening through distribution of preformed melanin, is carcinogenic, and suppresses the immune system.¹ Ultraviolet B (UVB) radiation (290 to 320 nm) causes delayed pigment darkening, the result of DNA damage and a compensatory increase in melanogenesis.² Chronic exposure to UVB is the most important factor in the development of skin cancers. Ultraviolet C (UVC) radiation (200 to 290 nm) is absorbed by the ozone layer and does not reach the earth's surface. Though midday UVR is 10% UVB and 90% UVA, UVB is 1,000 times more erythemogenic than UVA, making it the major culprit in skin carcinogenesis.² UVR induces genetic changes via chromosome damage and the inactivation of tumor suppressor genes such as p53. Skin types can be classified on the basis of response to UVR (Table 54-2).

II. CLINICAL PRESENTATION

A. Sunburn. Please see Chapter 42.

B. Indoor Tanning. The use of indoor tanning beds in the United States is a \$3 billion per year industry.¹ The sunlamps in these tanning units emit four times more UVA and two times more UVB than natural sunlight. This dose can produce erythema and melanogenesis but does not provide the protection of a naturally occurring tan, because there is no thickening of the stratum corneum nor is there an increase in the minimal erythema dose. The major concern regarding tanning beds is the carcinogenic effect of multiple doses of UVR.

C. Dermatoheliosis. Photoaging, caused by chronic exposure to UVR, is due to alterations in the collagen and elastic fibers in the papillary dermis. It can manifest in a myriad of ways including Milian citrine skin (diffusely yellow hue), poikiloderma, cysts and comedones on the face (Favre-Racouchot syndrome), colloid milium, cutis rhomboidalis nuchae (leathery skin with exaggerated skin markings on the neck), elastotic nodules on the helices and forearms, actinic purpura, and stellate pseudoscars (Fig. 54-1).

D. Photosensitivity

1. Photoallergy. Photoallergy requires prior sensitization, exposure to UVA light (UVB is less commonly implicated), and the administration of a photosensitizing systemic drug or an external contactant²

TABLE 54-1	Ultraviolet Radiation Bands	
	Wavelength (nm)	Significance
UVA	320–400	Immediate pigment darkening
UVB	290–320	Delayed pigment darkening Major source of carcinogenesis
UVC	200–290	Absorbed by the ozone layer

TABLE 54-2	Skin Types	
Type 1	Always burns	Never tans
Type 2	Burns readily	Tans minimally
Type 3	Burns moderately	Tans gradually
Type 4	Burns minimally	Tans moderately
Type 5	Rarely burns	Tans readily
Type 6	Never burns	Tans profusely



Figure 54-1. Solar elastosis: temple. (Image provided by Stedman’s.)



Figure 54-2. Drug photosensitivity eruption. Erythematous (exaggerated sunburn) reaction in a person who was taking demeclocycline (Declomycin) and fell asleep on the beach. (From Albert Einstein College of Medicine, Division of Dermatology, Bronx, New York.)

(Fig. 54-2). Clues to this diagnosis are medication history and the photodistribution of the skin findings (i.e., sparing of submental region). In a subset of patients, persistent photoallergy produces a chronic eczematous eruption, termed chronic actinic dermatitis, which persists even once the photosensitizer has been eliminated. These patients have broad-spectrum photosensitivity to both UVA and UVB light. Strict sun avoidance is key to treatment, though many patients also require systemic steroids or immunosuppressants.

2. **Phototoxicity.** Phototoxicity is much more common than photoallergy and does not require prior sensitization; it occurs in most patients exposed to the culpable drug, be it systemic or an external contactant.² Photoexposed areas develop a sunburn-like reaction that eventuates into hyperpigmentation. A subset is known as phytophotodermatitis and is specifically induced by contact with furocoumarins in plants such as celery and limes. Clues to this diagnosis are history and linear streaky lesions corresponding to areas of physical contact with the plant. Hyperpigmentation may persist for months (Table 54-3).
3. **Idiopathic Photosensitivity.** For idiopathic photosensitizing conditions such as polymorphous light eruption, actinic prurigo, and hydroa vacciniforme, sun avoidance and strict sunscreen use is key. Many skin and connective tissue diseases are exacerbated by UV radiation.

III. TREATMENT

- A. **Sunscreens.** Sunscreens have been shown to prevent ultraviolet-induced DNA damage. Regular use clearly prevents the development of nonmelanoma skin cancer, but its effect on the prevention or development of

TABLE 54-3 Common Photosensitizing Medications	
Photoallergy	Phototoxicity
Piroxicam	Doxycycline
Thiazide diuretics	Demeclocycline
Griseofulvin	Naproxen
Sulfonamides	Ibuprofen
Quinine/quinidine	Fluoroquinolones
	Amiodarone
	Psoralens
	Phenothiazines
	Voriconazole
	Furosemide

melanoma is controversial. A meta-analysis done in 2002 that included over 9,000 patients failed to show an association between sunscreen use and melanoma development.³ Chemical sunscreens block the penetration of UV radiation via absorption, while the physical sunscreens reflect UV radiation. Most sunscreens have their peak absorption in the UVB range.

The PABA (*para*-aminobenzoic acid) derivative padimate O is the most potent UVB blocker available, but due to the high incidence of allergic contact dermatitis (ACD), the second most potent UVB blocker, octyl methoxycinnamate, is the most common active ingredient in sunscreens.⁴ The benzophenone oxybenzone is a good UVA blocker as is menthyl anthranilate, but avobenzene, also known as Parsol 1789, provides the most thorough UVA coverage of all of the chemical blockers. The overall best UVA blockers are the physical blockers, zinc oxide and titanium dioxide (Table 54-4).

The sun protection factor (SPF) value is defined as the dose of UVR required to achieve minimal skin erythema after the application of 2 mg/cm²

TABLE 54-4 Sunscreen Ingredients		
Sunscreen Ingredients	UVA Protection	UVB Protection
<i>para</i> -Aminobenzoic acid derivatives		+++
Cinnamates		++
Salicylates		+
Benzophenones	++	++
Avobenzene	+++	
Zinc oxide	+++	+++
Titanium dioxide	+++	+++

TABLE 54-5 General Guidelines for Sunscreen Use

1. Select a sunscreen with an SPF of 30 or greater that has both UVA and UVB protection (broad spectrum)
2. Apply the sunscreen 20 min before sun exposure. Do not forget the ears, neck, and scalp
3. One ounce (enough to fill a shot glass) is needed in order to cover the entire body
4. Reapply every 1–2 h during outdoor activities and after swimming
5. Do not forget sun-protective clothing (hats, long-sleeve shirts, and sunglasses)
6. Avoid mid-day sun exposure (10 AM to 4 PM) even when using sunscreen
7. The American Academy of Pediatrics has determined that sunscreen use for infants less than 6 mo of age is acceptable if no other method of sun protection is available

of sunscreen divided by the dose of UVR needed to achieve erythema on unprotected skin.⁴ The SPF usually ranges from 2 (minimal protection) to 30+ (highest protection). SPF 2 gives 50% protection from UVR, SPF 15 produces 93% protection, and SPF 34 gives 97% protection. The average person only applies 25% to 75% of the recommended amount of sunscreen.⁵ Water-resistant labeling indicates that the SPF is maintained after two 20-minute immersions in water. Very water-resistant labeling implies that the SPF is maintained after four 20-minute immersions (Table 54-5).

The protection achieved by fabrics is expressed as the ultraviolet protection factor. Depending on material, stitch, color, moisture content, and chemical additives, clothing can provide a range of protection. Fabrics with tighter weaves, darker colors, synthetic fibers, and loose fit typically provide the greatest protection.

Sunscreen at times may lead to adverse effects. PABA may stain clothing yellow and cause ACD. Patients allergic to benzocaine, procaine, *para*-phenylenediamine, and sulfonamides may have allergic reactions to PABA. As the use of benzophenone-3 is increasing, it has become the number one contact photoallergen. Irritant contact dermatitis is much more common than ACD. Though sunlight is the major source of vitamin D synthesis in humans, minimal amounts of exposure to sun are sufficient to support its synthesis.⁴ In the elderly who are more at risk for the consequences of vitamin D deficiency, a daily multivitamin can be recommended.

B. Sunless Tanning. Dihydroxyacetone, the active ingredient in sunless tanning products, produces a brown-orange staining of the stratum corneum. There is no stimulation of melanin pigmentation.⁴ It is a safe alternative for patients who want a tanned appearance without the multitude of adverse health consequences of a natural tan (Table 54-6).

TABLE 54-6	Tips to Application of Sunless Tanning Lotion
<ol style="list-style-type: none">1. Lightly exfoliate the skin before application2. Apply every 2–3 h until the desired skin color is achieved3. Wash the hands well after application to prevent staining4. Elbows, knees, and ankles may take up more color than surrounding skin as may freckles5. Fabrics may become stained on contact with the product before it has dried6. Reapply every 3–5 d to maintain color	

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REFERENCES

1. Lim HW, Gilchrest BA, Cooper KP, et al. Sunlight, tanning booths and vitamin D. *J Am Acad Dermatol.* 2005;52:868.
2. James W, Berger T, Elston D. Dermatoses resulting from physical factors. In: *Andrews’ Diseases of the Skin.* 11th ed. Philadelphia, PA: Elsevier Inc.; 2011:23-34.
3. Huncharek M, Kupelnick B. Use of topical sunscreens and the risk of malignant melanoma: a meta-analysis of 9067 patients from 11 case control studies. *Am J Public Health.* 2002;92:173-177.
4. Levy S. Sunscreens. In: Wolverton S, ed. *Comprehensive Dermatologic Drug Therapy.* 2nd ed. Philadelphia, PA: Elsevier Inc.; 2007:703-716.
5. Azuridia RM, Pagliaro JA, Diffey BL, et al. Sunscreen application by photosensitive patients is inadequate for protection. *Br J Dermatol.* 1999;140:255-258.

Dressings are generally described as either primary or secondary. The primary dressing is applied directly adjacent to the wound bed to achieve functions such as tissue debridement, infection or inflammation control, or moisture balance. The secondary dressing is then placed against the primary dressing in order to secure and enhance the primary dressing, add absorbency or padding, relieve or add pressure, protect the wound, or provide additional therapeutic effects.

Table 55-1 lists advantages, disadvantages, and examples of common wound dressings by category. In addition, each major category of wound dressings is discussed individually in the text below—grouped according to wound moisture content (Fig. 55-1). In a wet wound environment, with moderate-to-heavy exudate, alginates, foams, hydrofibers, and gauze would be suitable choices, given that they are capable of absorbing excess fluid. These dressings would also be appropriate if the wound is infected. In a wound with appropriate moisture content without any signs of infection, films and hydrocolloids would likely be effective dressing choices. And lastly, for a dry wound without any signs of infection, a dressing that donates moisture, such as hydrogels, would be helpful to soften and debride dry necrotic tissue and support granulation. Additional types of hydrogels, such as hydrogel with silver (i.e., Silvasorb® gel), can be used to donate moisture as well as prevent infection.

DRESSING SELECTION

I. WET WOUNDS

A. Alginates. Alginates are highly absorbent, nonocclusive, biocompatible dressing derived from seaweed. They are sold as nonadhesive sheets, ropes, and alginate-tipped applicators. Alginates absorb sodium from the exudate or serum and release calcium into the wound, creating a beneficial hemostatic effect. The alginate gel helps maintain a moist wound environment after exudate has been absorbed, similar to the gel formed by hydrocolloids. The remaining gel, along with any exudate, debris, or bacteria that were absorbed by the gel, can be irrigated with saline at each dressing change.

Alginates are an effective choice for moderate to highly exuding wounds that are either infected or noninfected. The hemostatic properties also make alginates an ideal choice for heavily bleeding wounds. Alginates help maintain moisture balance in the wound and promote autolytic debridement. Thus, the alginates are commonly utilized for partial- and full-thickness wounds, venous stasis ulcers, diabetic ulcers, and other wounds with heavy exudate. The rope form of alginate is often used as packing for deep wounds, and the alginate-tipped applicators can be used in place of cotton-tipped applicators for probing a wound, because they are less likely to induce an inflammatory response in the wound if fibers are left behind.

TABLE 55-1 Common Wound Dressings by Category (Listed Alphabetically)

Category	Advantages	Disadvantages	Examples ^a
Alginates	<ol style="list-style-type: none">1. Highly absorbent2. Useful for infected wounds3. Useful in cavities4. Hemostatic5. Biocompatible6. Nonadherent7. Promote autolytic debridement	<ol style="list-style-type: none">1. ± Desiccation (painful if dries)2. Require secondary dressing3. ± Unpleasant odor4. Form a gel and require irrigation for removal	Algosteril Kaltostat Sorbsan
Films	<ol style="list-style-type: none">1. Retain moisture2. Bacterial barrier3. Waterproof4. Semipermeable to gas and vapor5. Transparent6. ± Adherent7. Promote autolytic debridement8. Reduce friction	<ol style="list-style-type: none">1. Nonabsorbent2. NOT for infected wounds3. ± Strip epithelium from a dry wound or fragile periwound4. ± Difficult to handle due to wrinkling	Bioclusive Blister film Omni-derm Opsite Tegaderm
Foams	<ol style="list-style-type: none">1. Moderately absorbent2. Useful for infected wounds3. Useful in cavities4. Conforms to contours5. Thermal insulation6. ± Adherent7. Promote autolytic debridement	<ol style="list-style-type: none">1. Can adhere to wound if exudate dries2. ± Secondary dressing3. ± Periwound maceration	Allernyn Lyof foam For cavities: Allernyn cavity Cavi-Care
Hydrocolloids	<ol style="list-style-type: none">1. Retain moisture2. Bacterial barrier3. Waterproof4. Semipermeable to gas and vapor5. Impermeable to urine and stool6. Adherent7. Promote autolytic debridement	<ol style="list-style-type: none">1. Minimal/moderate absorption2. NOT for infected wounds3. Unpleasant odor4. Form a gel and require irrigation for removal5. ± Periwound maceration6. ± Strip epithelium from fragile periwound7. ± Excess granulation	Comfeel Duoderm Restore Tegasorb

TABLE 55-1 (Continued)

Hydrogels	1. Rehydrate dry wounds	1. Minimal absorption	Amorphous Gel: Carrington gel Nu-Gel Sheets: Aquasorb Vigilon Hydrogel Gauze: CarraGauze
	2. Reduce pain	2. NOT for infected wounds	
	3. Reduce pressure	3. Poor bacterial barrier	
	4. Useful on necrotic tissue	4. \pm Periwound maceration	
	5. Semitransparent	5. Require secondary dressing	
	6. Nonadherent	6. Require frequent dressing changes	
	7. Promote autolytic debridement	7. Require irrigation for removal	

^aExamples listed are alphabetical and noninclusive, and the author does not endorse any particular brand.

Only the most typical characteristics are listed here, but can vary depending on the brand/form.

Source: Modified from Phillips TJ, Dover JS. Leg ulcers. *J Am Acad Dermatol*. 1991;25 (6 Pt 1):965-987.

If the wound is not very exudative, alginates could potentially cause a harmful desiccation; in this case, a dressing more suitable for lower amounts of exudate should be selected. For this reason, alginates should not be used on tendons, bones, or joint capsules, or on wounds with minimal or no exudate. As nonadherent dressings, alginates require a secondary dressing. In a noninfected wound, they can be left in place for several days or changed as necessary depending on the amount of exudate; however, in an infected wound, they must be changed daily. Dressing changes require saline irrigation to remove the residual gel.

B. Foams. Foam dressings are moderately absorbent, semioclusive polymer dressings, typically made of polyurethane or silicone. Foams are available as pads of various thicknesses, rolls, or foam packings for deep cavity wounds. Most foams are nonadherent; however, some contain an adhesive border. Foams contain two layers: the absorbent layer adjacent to the wound and the outer, semipermeable, barrier layer. The outer layer is similar to film dressings in that it is permeable to gas and water vapor, but impermeable to bacteria and fluids, thereby retaining moisture in the wound bed and preventing bacterial contamination.

Foam dressings are suitable for superficial or deep wounds, with mild, moderate, or heavy exudate, depending on the brand and thickness of foam. In addition, foams can be utilized on either infected or noninfected wounds. Foams provide padding as well as thermal insulation and promote autolytic debridement. Foams are utilized for a variety of wounds including partial- and full-thickness wounds, venous stasis ulcers, diabetic ulcers, superficial to deep pressure ulcers, and open surgical wounds. They are a preferred choice over the

familiar gauze dressing for packing open surgical wound because foams reduce pain, improve patient satisfaction, and reduce health-care costs associated with labor and materials for dressing changes.

In heavily exudating wounds, foams may cause maceration of the peri-wound skin, so it is best to use a barrier cream or skin protectant with foam dressings. If the exudate dries, foam dressings can adhere to and damage the wound; therefore, they should not be used on dry wounds. The nonadhesive foams require a secondary dressing. Foam dressing changes typically occur every 1 to 3 days, with a maximum use of 1 week, but foam dressings must be changed daily if the wound is infected.

C. Hydrofibers. Hydrofibers are highly absorbent dressings composed of carboxymethylcellulose fibers. Hydrofibers come in pads or ribbons that form a gel upon contact with the wound exudate. These dressings are an alternative choice for wounds with heavy exudate, with or without infection, and are sometimes used as packing in deep wounds. Hydrofibers require secondary dressings.

D. Gauze and Impregnated Gauze. Gauze is a nonocclusive, highly permeable, traditional wound dressing composed of woven cotton or nonwoven synthetic fibers, such as polyester and rayon. Gauze is inexpensive and readily available and comes in many varieties, including sterile and non-sterile rolls (2-, 6-, or 8-ply), pads, squares, packing strips, sheets, sponges, and swabs. Gauze ranges from minimally absorbent to highly absorbent; in general, nonwoven gauze and layered gauze are more absorbent. Gauze is available with or without an adhesive border. Gauze is also available impregnated with a variety of substances, such as sodium chloride (NaCl), paraffin, petrolatum, bismuth tribromophenate, iodine, zinc, and hydrogel, which can alter the properties and function of the dressings.

Gauze dressings can be applied on superficial or deep wounds, with mild, moderate, or heavy exudate, depending on the material and design. In addition, gauze can be utilized on either infected or noninfected wounds. Gauze dressings are a common choice of secondary dressings because they are inexpensive and highly absorbent. Roll gauze (i.e., Kerlix™) is beneficial as a secondary dressing to secure the primary dressing and avoid the use of adhesives on fragile or sensitive skin. In certain cases, gauze may also be appropriate as a primary dressing. For instance, when frequent dressing changes are required, such as infected and heavily exudating wounds, gauze may be an acceptable dressing selection. Also, gauze packing strips can be utilized to fill dead space in a wound, including cavities, undermining, and tunnels. Gauze packing strips are available in multiple widths as either plain packing strips or packing strips impregnated with iodoform, hydrogel, or polyhexamethylene biguanide. The packing strips should be loosely packed into the wound with the sterile technique.

Although often not the most effective method, wet-to-dry gauze dressings are sometimes used for mechanical debridement. This type of debridement can be quite detrimental to the wound and patient, as discussed in the debridement section earlier. When utilized for mechanical debridement, loose-weave gauze dressings, moistened with saline, trap debris and necrotic tissue as the dressing dries and the debris is physically removed at each dressing change, which typically occurs two or three times daily. However, the gauze may potentially adhere to and injure healthy tissue as well. Thus, removal of the gauze dressing

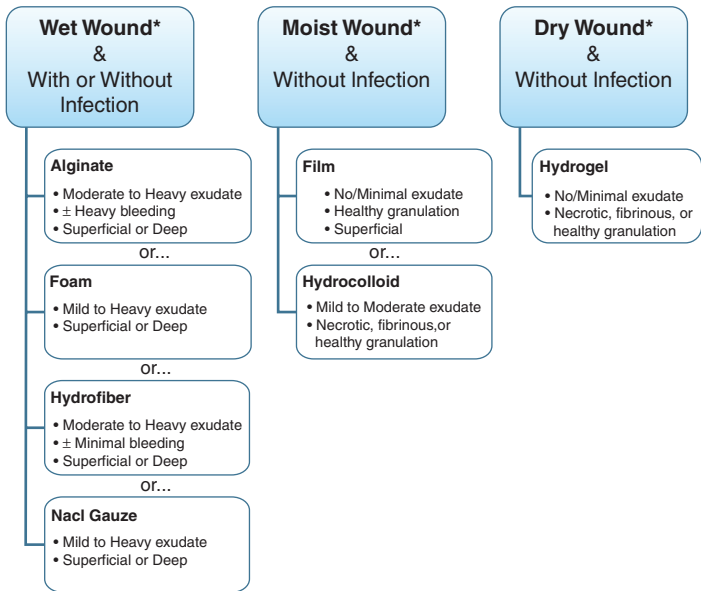


Figure 55-1. Dressing selection by wound moisture content and additional characteristics.[†] © Emily Bahram-ahi.

*The terms “wet”, “moist”, and “dry” are used to describe the wound moisture content. The term “moist” is used to describe a wound bed with a balanced moisture content, ideal for wound repair, whereas the term “wet” is used to describe a wound with an excess amount of moisture, and the term “dry” is used to describe a wound with too little moisture.

[†]In the first row of boxes, observable wound conditions are noted (moisture content and infection status). Below each of the three specified wound conditions (wet, moist, or dry), categories of dressings are listed alphabetically, each of which would be a potentially suitable choice for a wound observed to have those characteristics. However, these lists are noninclusive, and this information may vary depending on the brand or design of the dressing (© Emily Bahram-ahi).

may be severely painful for the patient and traumatic to the wound. In such cases, it may be necessary to wet the dressing with normal saline upon removal. This may result in ineffective debridement and impaired wound healing. In general, woven gauze is more difficult to remove than nonwoven gauze and it is also more likely to leave lint within the wound, which could create a harmful inflammatory reaction.

In addition, since gauze dressings are generally nonocclusive and do not retain moisture, they may dry out easily, causing desiccation of the wound and impaired wound healing. Therefore, gauze alone is not recommended for dry wounds. Standard gauze dressings also have a risk of causing maceration of the wound and periwound skin. Therefore, frequent dressing changes are often required to help prevent maceration and desiccation of the wound.

In general, impregnated gauzes are more occlusive, less permeable, and less adherent than plain gauze, which makes them less likely to dry out and

often easier and less painful to remove. The medicated gauzes may also provide additional benefits, such as antimicrobial properties, reduced adherence, and increased absorbency, and possibly some disadvantages, such as cytotoxicity, dermatitis, irritation, inflammation, and bacterial resistance, depending on each individual product. A few examples of impregnated gauze dressings are discussed below. Petrolatum-impregnated gauze is available as a nonadherent wound contact layer, which can help prevent dehydration of the wound as well as trauma and pain upon removal. Petrolatum-impregnated gauze dressings are sometimes useful on burns and granulating wound beds. They require a secondary dressing and can be combined with ointments or other products that are applied directly to the wound. Petrolatum-impregnated gauze is available alone (i.e., *Adaptic*®) or impregnated with the antiseptic 3% bismuth tribromophenate (i.e., *Xeroform*™). Another type of impregnated gauze dressing, NaCl-impregnated gauze (i.e., *Mesalt*®), is highly absorbent and is useful on heavily draining infected wounds. In addition, the zinc-impregnated gauze paste bandage, known as the Unna boot, is used to apply compression to treat venous insufficiency ulcers and is also discussed in the section above on factors that impede wound healing.

II. MOIST WOUNDS

A. Films. Film dressings are thin, transparent, polyurethane or polyethylene polymer dressings. Typically, films come in self-adhesive sheets that adhere to the dry periwound skin but not the wet wound bed, although some types of films are nonadhesive or have adhesive-free zones. Films are semipermeable, semioclusive, waterproof dressings, which permit the exchange of gases and water vapor, such as oxygen and carbon dioxide, but prevent the transport of larger particles, such as bacteria, debris, fluid, and protein.

Film dressings are nonabsorbent and are ideal for noninfected, superficial, moist wounds with very minimal exudate. The entrapment of wound fluids and moisture retention by film dressings has been shown to help promote autolytic debridement and formation of granulation tissue. Films are commonly used for venous catheter sites, superficial wounds, partial-thickness wounds, burns, dermabrasion, laser wounds, skin tears, skin grafts, graft donor sites, and areas of friction. In addition, healthy granulation tissue is best supported by dressings that retain moisture, including films, hydrocolloids, and hydrogels.

If the wound is dry or the periwound skin is fragile, an adhesive film can damage or strip epithelium if removed before falling off spontaneously. Therefore, films are sometimes used in combination with hydrogels to maintain a moist environment in a dry wound and skin protectants to protect the periwound skin from maceration or damage. Films are not suitable for infected wounds. Film dressings may typically be left in place for 5 to 7 days; however, maintaining a good seal around the wound is important in order to prevent contamination, so if a wrinkle or channel develops, the dressing must be changed.

B. Hydrocolloids. Hydrocolloids are occlusive, self-adhesive dressings composed of colloidal particles of proteins (i.e., gelatin), polysaccharides (i.e., pectin and carboxymethylcellulose), and polymers within a matrix, with a foam or film backing. They are most frequently sold as flexible sheets or wafers that can be modified to fit the size of the wound. Upon contact

with wound exudate, hydrocolloids absorb and retain fluid in the wound and become a fetid, thick, yellow-brown, colloidal gel, which can resemble purulent drainage, similar to the gel formed by alginate dressings. The residual gel helps maintain a moist environment in the wound, which is beneficial for healing, and can be irrigated with saline at each dressing change.

Hydrocolloids are most suitable for noninfected, moist wounds with a mild-to-moderate amount of exudate. Absorptive capacity varies depending on the brand of hydrocolloid. Due to their occlusive nature, they provide a good bacterial barrier and are impermeable to urine and stool, originally used with ostomy products. Hydrocolloids also retain moisture within a wound, thereby promoting autolytic debridement. Thus, they are effective on necrotic (slough or eschar), fibrinous, or healthy granulation tissue. Hydrocolloids, such as the well-known DuoDerm®, are commonly used to treat pressure ulcers. In addition, they are effective for the treatment of partial- and full-thickness wounds, burns, venous ulcers, and blistering or inflammatory conditions.

Care must be taken to prevent maceration of the periwound tissues as wound exudate is absorbed. In addition, hydrocolloids have a potential risk of stimulating excess granulation tissue formation. Hydrocolloids are not suitable for infected wounds. Dressing changes occur every 2 to 7 days and require saline irrigation to remove the residual gel.

III. DRY WOUNDS

A. Hydrogels. Hydrogels contain a high concentration of water within a hydrophilic polymer. They are available in sheets, amorphous gels, and impregnated gauzes. Hydrogels are able to donate water to rehydrate a dry wound and soften necrotic tissue. Since hydrogels are permeable to gases, fluids, and bacteria, they are sometimes packaged with a film backing that is impermeable to fluids and bacteria. They can also be used in combination with antimicrobial agents to reduce the bacterial burden or protective ointments on the periwound skin to prevent maceration.

Hydrogels, with minimal absorptive capacity, are ideal for dry wound environments with healthy granulation tissue, yellow slough, or black eschar and absent or very minimal exudate. Hydrogels are commonly used for partial- or full-thickness wounds, burns, chemical wounds, blisters, ulcers, skin tears, graft donor sites, and wounds with exposed bone or tendon. Hydrogels are cool upon contact and have a pain-relieving effect.

If left in place too long, hydrogel dressings can result in an undesirable desiccation of the wound or sometimes maceration of the periwound skin. Hydrogels are nonadherent and typically require a secondary dressing. Hydrogels are not suitable for infected wounds. In addition, hydrogels typically require frequent dressing changes, every 24 to 72 hours, with saline irrigation to remove the gel.

EPITHELIAL EDGE ADVANCEMENT

The final step of wound bed preparation involves evaluation and preparation of the wound edge and periwound skin in order to promote epithelial edge advancement and wound closure. Epithelial edge advancement, the final stage of wound repair,

refers to epithelialization of the wound and a reduction in wound size. In the process of epithelialization, keratinocytes proliferate and migrate from the wound margin across the wound. Therefore, an intact wound edge may help promote epithelialization and enhance wound repair. Once the patient, wound bed, and wound edge are optimized for healing, epithelialization and wound closure can progress. Preparation of the epithelial edge involves three steps: (1) consistent monitoring and assessment, (2) debridement of nonviable tissues, and (3) protection of the periwound skin.

The periwound skin is commonly described as viable, hyperkeratotic (calluses or corns), macerated (pale, softened, broken-down, devitalized skin due to excess exposure to moisture), inflamed, edematous, indurated, or fluctuant. Hyperkeratosis is a thickening of the stratum corneum associated with areas of elevated pressure or friction. Calluses and corns develop as a result of hyperkeratosis. It is a physiologic response, but it can become pathologic and lead to problems such as neuropathic plantar foot ulceration in diabetic patients. As discussed in the section on tissue management and debridement, nonviable tissue in and around the wound can delay wound repair and frequent removal of nonviable tissue leads to improved healing rates. Therefore, debridement of hyperkeratotic and macerated periwound tissue may be beneficial.

Skin care products used to protect the periwound skin include skin sealants, moisture barriers, and moisturizers. Most of these products are only intended for use on intact skin; however, some can be used on damaged skin as well. Topical skin protectants are typically referred to as either skin sealants or moisture barriers. Skin sealants are available as sprays or wipes that can be applied to all intact skin around wounds being treated with moisture-retentive dressings or areas of skin exposed to excess moisture. Skin sealants are composed of various polymers dissolved in a fast-drying solution that evaporates upon contact with skin, leaving behind a thin barrier film. The solution may be alcohol-based and only appropriate for use on intact skin due to cytotoxicity (i.e., Bard® protective barrier film wipes) or non-alcohol-based and acceptable for use on damaged and intact skin (i.e., 3M™ Cavilon™ no-sting barrier film spray and wipes). Skin sealants provide a protective coating to help prevent periwound maceration, breakdown, and adhesive tape trauma. Placed between intact periwound skin and an adhesive wound dressing, a skin sealant not only protects the skin from trauma or irritation that may be caused by the adhesive, but also helps create a better edge seal.

Moisture barriers, on the other hand, are ointments, creams, gels, or pastes composed of petrolatum, zinc, or dimethicone. Moisture barriers are commonly used to prevent or sometimes treat rashes or skin breakdown due to excess moisture from wound drainage, incontinence, or perspiration. Since moisture barriers are typically oily and reduce the adherence of dressings and tapes, they are not generally used where adhesives are required. Moisture barriers can be beneficial in the genital and rectal regions to prevent or treat skin irritation or breakdown caused by bodily fluids. Only certain moisture barriers are acceptable for use on nonintact skin.

Dry skin reduces the barrier function of the skin and can cause chapping, cracking, fissuring, and an increased risk of infection. Therefore, moisturizers, which are often petrolatum-based, are commonly used to prevent and treat dry skin. Other options to treat dry skin include creams, lotions, and ointments.

ADVANCED DRESSINGS

Advanced therapies should be considered if the wound area has not significantly decreased (by 30% to 50%) after 3 to 4 weeks of adequate standard treatment. In addition to considering other options for wound therapy, alternative compounding factors must be addressed. A large variety of advanced dressing techniques are available and new dressings continue to be developed and studied; however, these advanced dressings are beyond the scope of this chapter. The reader should refer to other texts for more in-depth information about advanced dressings. As in this entire chapter, product brand names are provided for example purposes only, are noninclusive lists, and are not endorsed by the author.

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Suggested Readings

- Agrawal K, Chauhan N. Pressure ulcers: back to the basics. *Indian J Plast Surg.* 2012;45(2):244-254.
- Armstrong DG, Nguyen HC, Lavery LA, van Schie CH, Boulton AJ, Harkless LB. Off-loading the diabetic foot wound: a randomized clinical trial. *Diabetes Care.* 2001;24(6):1019-1022.
- Falabella AF. Debridement and wound bed preparation. *Dermatol Ther.* 2006;19(6):317-325.
- O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. *Cochrane Database Syst Rev.* 2012;(11). Art. No.: CD000265. doi:10.1002/14651858.CD000265.pub3.
- Phillips TJ, Machado F, Trout R, Porter J, Olin J, Falanga V. Prognostic indicators in venous ulcers. *J Am Acad Dermatol.* 2000;43(4):627-630.
- Schultz GS, Sibbald RG, Falanga V, et al. Wound bed preparation: a systematic approach to wound management. *Wound Repair Regen.* 2003;11(1 Suppl):S1-S28.
- Zarchi K, Jemec GB. The efficacy of maggot debridement therapy—a review of comparative clinical trials. *Int Wound J.* 2012;9(5):469-477.

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